LEVAQUIN® Formulary Dossier
(Levofloxacin Tablets/Injection)
(Levofloxacin in 5% Dextrose Injection)

- **This document is presented to the Montana Medicaid.**
- **Use of this document is intended only for review by Montana Medicaid in evaluation of Levaquin® (levofloxacin) for formulary consideration.**

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INTRODUCTION

LEVAQUIN® TABLETS/INJECTION
(LEVOFLOXACIN TABLETS AND INJECTION)
(LEVOFLOXACIN IN 5% DEXTROSE) INJECTION

- Synthetic, broad-spectrum, bactericidal antimicrobial with an antibacterial spectrum that covers a wide variety of gram-positive, gram-negative, and atypical pathogens.
- Levofloxacin was the first fluoroquinolone indicated for typical and atypical pathogens commonly associated with CAP.
- Levofloxacin, the active (-)-(S)- enantiomer of ofloxacin, has been available in Japan and South Korea since 1993 and in the US since December 1996, with more than 300 million patients treated worldwide.
- Levofloxacin has broad clinical utility in the treatment of various respiratory, urinary tract, and skin infections that in the past required lengthy hospitalizations for treatment with parenteral agents.
- Levofloxacin is approved for ten indications in the U.S., including acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, nosocomial pneumonia, community-acquired pneumonia (including multi-drug resistant *Streptococcus pneumoniae*, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, chronic bacterial prostatitis, acute pyelonephritis, complicated urinary tract infections, and uncomplicated urinary tract infections.
- Levofloxacin is administered in once daily doses of 250 mg, 500 mg, or 750 mg for durations of 3 to 28 days depending on the indication.
- Levofloxacin is the first fluoroquinolone approved for a short duration regimen of 5 days for the treatment of community-acquired pneumonia.
- The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.
- Levofloxacin concentrations in most tissues are higher than in plasma. In lung tissue homogenate, concentrations are 2.5 to 5 fold higher than plasma.
- Levofloxacin undergoes limited metabolism. Dosage adjustments are recommended in patients with a creatinine clearance < 50 mL/min.
- The pharmacoeconomics of levofloxacin use has been evaluated for patients treated for CAP. In these analyses, levofloxacin has allowed rapid conversion from IV to oral administration, which results in cost savings.
- In summary, levofloxacin is a safe and effective therapeutic agent for bacterial infections caused by a wide variety of gram-positive and gram-negative aerobic pathogens.

2. PRODUCT INFORMATION

A. PRODUCT DESCRIPTION

1. **Generic/Brand name:** Levofloxacin/Levaquin®

2. **Therapeutic class:** Fluoroquinolones

3. **Dosage Forms, Strengths, Package Size, National Drug Code (NDC), and AWP Costs:**

Dosage Forms	Strengths	Package Size	NDC	AWP UNIT Costs
Tablets	250 mg	• Bottles of 50	• 0045-1520-50	$ 9.22
		• Unit-dose/100	• 0045-1520-10	$ 9.29
	500 mg	• Bottles of 50	• 0045-1525-50	$ 10.57
		• Unit-dose/100	• 0045-1525-10	$ 10.63
	750 mg	• Bottles of 20 • Unit-dose/100 • LEVA-Pak Unit-dose/5	• 0045-1530-20 • 0045-1530-10 • 0045-1530-05	$ 20.91 $ 19.93 $19.93
Single-Use Vials	25 mg/ml	• 20 ml	• 0045-0069-51	$ 2.28
	25 mg/ml	• 30 ml	• 0045-0065-55	$ 2.02
Premix in Flexible Containers	250 mg (5 mg/ml)	• 50 ml	• 0045-0067-01	$ 0.46
	500 mg (5 mg/ml)	• 100 ml	• 0045-0068-01	$ 0.46
	750 mg (5 mg/ml)	• 150 ml	• 0045-0066-01	$ 0.40

*AWP prices as of 3/04

4. **Copy of the Official Product Labeling:** See accompanying PI

5. **AHFS Drug Classification:** 8:22

6. **FDA Approved Indications:** Levofloxacin is indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed in the table below.

Indications	Organism(s)
Acute maxillary sinusitis	*Streptococcus pneumoniae; Haemophilus influenzae; Moraxella catarrhalis*
Acute bacterial exacerbation of chronic bronchitis	*Staphylococcus aureus; Streptococcus pneumoniae; Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis*
Nosocomial Pneumonia*	Methicillin-susceptible *Staphylococcus aureus; Pseudomonas aeruginosa; Serratia marcescens; Escherichia coli; Klebsiella pneumoniae; Haemophilus influenzae;* or *Streptococcus pneumoniae*
Community-acquired pneumonia	*Staphylococcus aureus; Streptococcus pneumoniae* (including multi-drug resistant strains)***; Haemophilus influenzae; Haemophilus parainfluenzae; Klebsiella pneumoniae; Moraxella catarrhalis; Chlamydia*

	pneumoniae; Legionella pneumophilia; Mycoplasma pneumoniae
Uncomplicated skin and skin structure infections	*Staphylococcus aureus; Streptococcus pyogenes*
Complicated skin and skin structure infections	Methicillin-susceptible *staphylococcus aureus; Enterococcus faecalis; Streptococcus pyogenes; Proteus mirabilis*
Chronic bacterial prostatitis	*Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis*
Acute pyelonephritis (mild to moderate)	*Escherichia coli*
Uncomplicated urinary tract infections (mild to moderate)	*Escherichia coli; Klebsiella pneumoniae; Staphylococcus saprophyticus*
Complicated urinary tract infections	*Enterococcus faecalis; Enterobacter cloacae; Escherichia coli; Klebsiella pneumoniae; Proteus mirabilis; Pseudomonas aeruginosa*

*Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended

**MDRSP (Multi-drug resistant Streptococcus pneumoniae) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC value ≥ 2 mg/ml), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

7. **Pharmacology:** As with other fluoroquinolones, levofloxacin produces its antibacterial activity by targeting certain enzymes involved in the DNA replication. The mechanism of action of levofloxacin involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair, and recombination.

8. **Pharmacokinetics:** Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. As demonstrated in comparative bioavailability pharmacokinetic trials, both formulations are equivalent in the extent of absorption. Other than a transient and slight difference in peak plasma levels, the plasma concentration profiles from the two routes of administration are nearly super-imposable in the post peak, distribution-elimination phase. Therefore, the oral and intravenous routes of administration can be considered interchangeable.

Absorption	• Rapid and essentially complete absorption after oral administration • Absolute bioavailability of 500 mg and 750 mg tablets is approximately 99% • Steady-state conditions are reached within 48 hours following 500 mg or 750 mg once daily dosing regimens
Distribution	• The mean volume of distribution generally ranges from 74-112L after single and multiple 500 mg and 750 mg doses • Levofloxacin has been shown to be approximately 24-38% bound to serum proteins, the main one being albumin • Concentration of drug after oral administration is usually substantially higher in most tissues and body fluids than plasma levels • Pharmacokinetic studies of healthy adults have documented the excellent penetration of levofloxacin into lung tissue with lung concentrations exceeding plasma concentrations by 2 to 5 fold

Metabolism	• Levofloxacin is minimally metabolized by the liver • Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin
Elimination	• After oral administration, approximately 87% of an administered dose is recovered as unchanged drug in the urine within 48 hours • Less than 5% of an administered dose was recovered in urine as desmethyl and N-oxide metabolites • Less than 4% of the dose is recovered in feces within 72 hours • The mean terminal plasma elimination half-life of levofloxacin is approximately 6-8 hours following single or multiple doses given orally or intravenously (elimination half-lives are increased with decreasing renal clearance) • Dosage adjustments for levofloxacin are recommended in patients with a creatinine clearance <50 ml/min

- **Comparative Data:**

Lubasch et al conducted an open, randomized, six-period crossover study to compare the pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin in 12 healthy volunteers. The volunteers (6 men, 6 women) were given single oral doses of 250 mg ciprofloxacin, 400 mg gatifloxacin, 600 mg grepafloxacin, 500 mg levofloxacin, 400 mg moxifloxacin, or 200 mg trovafloxacin with a 2-week washout period between each dose. Serum and urine concentrations were measured before and at time points up to 48 h after administration. Peak plasma concentrations and total areas under the curve are summarized in the table below. Side effects were reported during examinations at 12, 24, and 48 hours after medication administration and ECG was performed before and 12 h after each medication. No serious adverse events were reported and no changes in ECG were noted during the study period (Lubasch et al., *Antimicrob Agents Chemother* 2000).

COMPARATIVE PHARMACOKINETICS FROM LUBASCH ET AL

	C_{max} μg/ml/70 kg	T_{max} (Hr)	$T_{1/2}$ (Hr)	AUC_{tot} μg*hr/ml/70 kg	Total Urinary Recovery (% of dose)
Levofloxacin	6.21± 1.34	0.8 ± 0.38	6.95 ± 0.81	44.8 ± 4.4	75.9 ± 11.6
Moxifloxacin	4.34 ± 1.61	1.02 ± 0.72	9.15 ± 1.62	39.3 ± 5.53	19.9 ± 4.55
Gatifloxacin	3.42 ± 0.74	1.49 ± 0.65	6.52 ± 0.87	30 ± 3.8	76.9 ± 5.6
Ciprofloxacin	1.5 ± 0.43	0.78 ± 0.33	5.37 ± 0.82	5.75 ± 1.25	40.8 ± 7.48

Gotfried et al. performed a multiple-dose, open-label, randomized pharmacokinetic study to compare the steady-state plasma, epithelial lining fluid, and alveolar macrophage concentrations of levofloxacin and ciprofloxacin. Thirty-six healthy, nonsmoking, adult subjects were randomized to receive either oral ciprofloxacin 500 mg q 12 h for nine doses or oral levofloxacin 500 mg or 750 mg q 24 h for 5 doses. Drug concentrations were determined at 4 h, 12 h, and 24 h after the last administered dose of the antibiotic by performing venipuncture, bronchoscopy, and bronchoalveolar lavage. For levofloxacin 500 mg and 750 mg, steady-state plasma and epithelial lining fluid

concentrations were significantly higher than ciprofloxacin 500 mg. Mean epithelial lining fluid concentrations for levofloxacin were similar or higher than plasma concentrations and epithelial lining fluid concentrations were lower for ciprofloxacin compared to plasma concentrations. Steady-state alveolar macrophage concentrations for levofloxacin and ciprofloxacin were significantly higher when compared to simultaneous plasma and epithelial lining fluid concentrations throughout the 12-h period after drug administration (Gotfried et al., *CHEST* 2001).

Rodvold et al compared the concentrations of levofloxacin and azithromycin in steady-state plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM) after intravenous administration in a randomized, open-label, single-center study. Thirty-six nonsmoking, healthy adult subjects (aged 18-55) were randomized to receive either intravenous levofloxacin (500 or 750 mg) or azithromycin (500 mg) once daily for five doses. Each subject underwent standardized bronchoscopy and bronchoalveolar lavage (BAL) at either 4, 12, or 24 hours following the start of the last intravenous infusion of antibiotic. At the 4 hour sampling time (approximating the peak), the plasma, ELF, and AM concentrations (± SD) for levofloxacin 500 mg were: 4.74 ±1.37, 11.01±4.52, and 83.9±53.2 µg/mL, respectively. The respective concentrations for levofloxacin 750 mg were: 6.55±1.65, 12.94±1.21, and 81.7±37.0 µg/mL. The respective concentrations for azithromycin 500 mg were: 0.37±0.10, 1.70±0.74, and 649.9±259.1 µg/mL. The concentrations of 500 and 750 mg levofloxacin in steady-state plasma were significantly higher than those of 500 mg azithromycin during the entire 24-hour study period. The mean concentrations of levofloxacin and azithromycin in ELF were higher than those in plasma except at the 24-hour sampling time of 750 mg levofloxacin. Levofloxacin and azithromycin achieved significantly higher steady-state concentrations in AM than simultaneous concentrations in plasma and ELF throughout the 24-hour period after drug administration (Rodvold et al, *Antimicrob Agents Chemother* 2003).

- **Special Populations:**

Age/Gender: The influences of age and gender were evaluated in a parallel design study in healthy subjects receiving a single 500 mg oral dose of levofloxacin.
Six young men and six young women (age 18 to 40 years), and six elderly men and six elderly women (age 65 years), were studied. The bioavailability of levofloxacin was not affected by age or gender when the different creatinine clearances were considered. The apparent volume of distribution was approximately 18% lower in elderly subjects than in young subjects, and 15% lower in women than in men. These reductions were expected based on the extensive distribution of levofloxacin throughout the body and the particular low body-weight characteristics of women and the elderly. In all subjects, the mean peak plasma concentration of levofloxacin was reached approximately 1.5 hours after drug administration. Renal clearance accounted for approximately 77% of total body clearance.

Therefore, dose adjustment should be based on a patient's creatinine clearance rather than age or gender. The mean adjusted pharmacokinetic parameters of the four study groups are presented in the table below (Chien et al., Antimicrobial Agents and Chemotherapy 1997).

Summary of the Adjusted Means of Levofloxacin PK Parameters by Age and Gender

Parameter	Men	Women	Young	Elderly
C max (µg/mL)	5.77	6.71	6.26	6.22
AUC (0-∞) (µg•h/mL)	60.6	61.6	66.0	56.2
CL/F (mL/min)	160	143	157	146
CL R (mL/min)	120	112	117	115

The adjusted means were obtained as the predicted values of the pharmacokinetic parameters corresponding to an average creatinine clearance value. Abbreviations: C max = peak plasma concentration; AUC (0-¥) = area under the plasma concentration vs time curve from time zero to infinity; CL/F = total body clearance; CL R = renal clearance of drug.

Pediatric: Safety and effectiveness in pediatric patients and adolescents below age of 18 years have not been established.

Chien et al conducted two randomized, open-label, parallel group, single-dose, multicenter Phase I studies to assess single-dose pharmacokinetics and tolerability of intravenous levofloxacin in pediatric patients (n=40). Study subjects included children 6 months to 16 years of age with normal renal function who were at a high risk for bacterial infections or with documented or presumed bacterial infection being treated with antibiotics other than quinolones. A single dose of levofloxacin 7mg/kg (not to exceed 500mg) was infused at a constant rate over 1 hour. Drug-concentration versus time profiles were superimposable between the 0.5-2yr and 2-5yr age groups, the 5-8yr and 8-10yr age groups, and the 10-12yr and 12-16yr age groups. Peak exposure (C_{max}) and volume of distribution (Vd) were similar among all age groups. However, clearance (CL) did yield age-related alterations. The clearance in the study subjects decreased with increasing age, thereby increasing total systemic exposure (AUC) with increasing age. Twenty-four hours post-dose, approximately 72-79% of the dose in subjects providing urine samples was excreted unchanged in the urine. The table below summarizes the pharmacokinetic estimates in the pediatric and adult patients.

Summary of Pharmacokinetic Estimates (mean ± SD)

Age (years)	# of Subjects	C_{max} (ug/ml)	$T_{1/2}$ (hour)	AUC (ug*h/ml)	Vd (l/kg)	CL (l/h/kg)	CLr (l/h/kg)
5 age groups							
0.5-2	6	5.19 ± 1.26	4.1 ± 1.3	21.5 ± 6.12	1.56 ± 0.30	0.35 ± 0.13	NA
2-5	7	6.02 ± 1.07	4.0 ± 0.8	22.7 ± 4.66	1.50 ± 0.21	0.32 ± 0.08	NA
5-10	9	6.11 ± 0.88	4.8 ± 0.8	29.2 ± 6.40	1.57 ± 0.44	0.25 ± 0.05	0.18 ± 0.07
10-12	7	6.12 ± 1.19	5.4 ± 0.8	39.8 ± 11.3	1.44 ± 0.35	0.19 ± 0.05	0.15 ± 0.06
12-16	11	6.15 ± 1.55	6.0 ± 2.1	40.5 ± 7.56	1.56 ± 0.53	0.18 ± 0.03	0.11 ± 0.04
3 age groups							
0.5-5	13	5.63 ± 1.19	4.0 ± 1.0	22.2 ± 5.18	1.53 ± 0.25	0.34 ± 0.10	NA
5-10	10	6.11 ± 0.88	4.8 ± 0.8	29.2 ± 6.40	1.57 ± 0.44	0.25 ± 0.05	0.18 ± 0.07
10-16	19	6.14 ± 1.36	5.8 ± 1.7	40.2 ± 8.97	1.51 ± 0.46	0.18 ± 0.04	0.12 ± 0.05
Adults, single 500mg IV dose							
18-45	23	6.18 ± 1.04	6.0 ± 1.0	48.3 ± 5.40	1.27 ± 0.12	0.15 ± 0.02	NA

According to the investigators, the treatment-emergent adverse events were mild or moderate in severity and the majority were deemed not to be related to levofloxacin. However, seven subjects did experience an adverse event considered to be a result of the study drug. No joint related adverse events and no clinically significant alterations in laboratory values from predose to postdose were reported. The authors proposed pediatric dosing regimens (Table 2) for safety and efficacy evaluations in the treatment of community acquired pneumonia (CAP) and urinary tract infections (UTIs) based on the following criteria: Cmax and AUC levels which do not exceed those that are safe and effective in adults, a steady state Cmax/MIC ratio which has been effective in adults, and approximating the steady state AUC/MIC that has been related to the effectiveness in adults (Chien et al., 41st *ICAAC* 2001).

Race: The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 nonwhite. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Insufficiency: The pharmacokinetics of levofloxacin are altered in renally impaired patients, and the degree of alteration is related to the patient's creatinine clearance (table).

Dosage adjustments are necessary once the creatinine clearance is below 50 mL/min.

In renally impaired patients with decreasing creatinine clearance, the half-life of levofloxacin increases, the mean urinary excretion decreases, and the total body clearance decreases. Neither continuous ambulatory peritoneal dialysis (CAPD) nor hemodialysis removes levofloxacin efficiently from the body. Therefore, supplemental dosing is not necessary. To prevent accumulation of levofloxacin in renally impaired patients, simple dosage adjustments are required (SEE DOSAGE AND ADMINSTRATION).

Levofloxacin PK Parameters in Renally Impaired Male and Female Subjects Following a Single Oral 500-mg Dose

Parameter (Mean ± SD)	CL_{CR} 50-80 mL/min (n=3)	CL_{CR} 20-49 mL/min (n=8)	CL_{CR} <20 mL/min (n=6)	Hemodialysis (n=4)	CAPD (n=4)
C_{max} (µg/mL)	7.52 ± 1.75	7.10 ± 3.09	8.18 ± 2.56	5.71 ± 0.99	6.93 ± 2.31
T_{max} (h)	1.5 ± 0.5	2.1 ± 1.3	1.1 ± 1.0	2.8 ± 2.2	1.4 ± 1.1
$AUC_{(0-t)}$ (µg•h/mL)	93 ± 12	173 ± 57	252 ± 76	NA	NA
$AUC_{(0-\infty)}$ (µg•h/mL)	96 ± 12	182 ± 63	263 ± 72	NA	NA
CL/F (mL/min)	88 ± 10	51 ± 19	33 ± 8	NA	NA
$T_{1/2}$ (h)	9.1 ± 0.9	26.6 ± 10.2	34.8 ± 5.5	76.1 ± 41.5*	50.7 ± 23.8*
Ae%	61 ± 12	35 ± 12	16 ± 8	NA	NA
CL R (mL/min)	57 ± 8	26 ± 13	13 ± 3	NA	NA
CL d (mL/min)	NA	NA	NA	219 ± 25	5.0 ± 0.9

*Values for $T_{1/2}$ were estimated from the levofloxacin plasma concentration profiles, including times when these subjects were receiving dialysis; therefore, these parameters represent elimination by a combination of endogenous and exogenous processes. Abbreviations: CLCR = creatinine clearance; CAPD = continuous ambulatory peritoneal dialysis; Cmax = peak plasma concentration; Tmax = time of C max ; AUC(0-t) = area under the plasma concentration vs time curve from time zero to the time of the last measurable plasma concentration; CL/F = total body clearance of drug from plasma; $T_{1/2}$ = elimination half-life; Ae% = percent of dose recovered in the urine; CLR = renal clearance of drug; CL d = clearance by dialysis; AUC(0-24) = area under the plasma concentration vs time curve from time zero to 24 hours.

Hepatic Insufficiency: Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

HIV-Positive Patients: Levofloxacin pharmacokinetics after 750-mg and 1000-mg extended-interval regimens in patients infected with human immunodeficiency virus were consistent with those observed in healthy subjects (currently, the highest indicated dosage for levofloxacin is 750-mg for complicated SSSIs).

9. **Contraindications:** The use of LEVAQUIN is contraindicated in patients with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

10. **Warnings: THE SAFETY AND EFFICACY OF LEVAQUIN IN CHILDREN, ADOLESCENTS (< 18 YEARS OF AGE), PREGNANT WOMEN, AND NURSING MOTHERS HAVE NOT BEEN ESTABLISHED.**

    Pseudomembranous colitis has been reported with nearly all-antibacterial agents, including levofloxacin, and may range in severity from mild to life threatening. Therefore, it is important to

consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

- Musculo-Skeletal System Disorders

  Ruptures of the shoulder, hand or Achilles tendons that require surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

Yee et al conducted a retrospective, cohort, observational study to identify the incidence and relative risk of tendon or joint disorders (TJDs) associated with selected fluoroquinolones (ofloxacin, levofloxacin, and ciprofloxacin) compared to azithromycin (control group) in children < 19 years of age. Information regarding children who were exposed to either ofloxacin (n=1905), levofloxacin (n=38), ciprofloxacin (n=5904), or azithromycin (n=20,283) was obtained from the United HealthCare Research Database from January 1, 1992 to June 30, 1998. A list of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9cm) claims diagnoses was utilized to screen for potential TJDs that occurred within 60 days of having been prescribed the respective antibiotics. Among 576 potential cases identified, the physicians verified (based on review of medical record abstracts) the TJD diagnosis in 168 cases. The incidences of potential TJDs associated with ofloxacin, levofloxacin, ciprofloxacin, and azithromycin were 1.7%, 2.6%, 2.2%, and 2.0%, respectively. However, the incidence of physician verified TJDs associated with ofloxacin, levofloxacin, ciprofloxacin, and azithromycin therapies was 0.82%, 0.8%, 0.82%, and 0.78%, respectively. The crude relative risk for physician verified TJDs for ofloxacin, levofloxacin, and ciprofloxacin compared to azithromycin is presented as follows:

Fluoroquinolones Prescribed	Crude Risk for Verified TJDs
Ofloxacin	1.04 (95% CI, 0.59 – 1.84)
Ciprofloxacin	1.04 (95% CI, 0.72 – 1.51)
Ofloxacin, levofloxacin or ciprofloxacin	1.04 (95% CI, 0.75 – 1.45)

The relative risk for levofloxacin compared to azithromycin was not calculated due to a small number of children who were prescribed levofloxacin (n=38). The adjusted relative risk based on age, sex, and location of TJDs was similar to the crude relative risk of corresponding antibiotics. The authors concluded that this retrospective analysis suggested that TJDs occur rarely in children who were exposed to fluoroquinolones and the incidence of TJDs occurring within 60 days of prescribed fluoroquinolones was comparable to the control group, azithromycin. However, these findings do not imply that use of fluoroquinolones in children is not associated with an increase risk for TJDs.

The authors also suggested that large prospective studies should be conducted to further evaluate the incidence and risks of TJDs associated with fluoroquinolones in the pediatric population (Yee et al., *Pediatr Dis* 2002).

A case-control study that assessed 46,776 users of fluoroquinolones and 10,000 control patients was conducted to evaluate the Achilles tendon disorders associated with fluoroquinolone therapy. The IMS Health database (a large UK general practice database) provided data for the analysis between July 1, 1992 and June 30, 1998. The use of fluoroquinolones was categorized according to current use (occurrence of tendon disorder between the start of the fluoroquinolone therapy and the calculated end date plus 30 days), recent use (calculated end date between 30 and 90 days before the occurrence of the disorder), past use (calculated end date > 90 days before the occurrence of the disorder), and no use. Of the 46,776 patients exposed to fluoroquinolones, 704 developed Achilles tendinitis and 38 experienced Achilles tendon rupture. The adjusted relative risk (based on age, sex, number of doctor visits, use of corticosteroids, calendar year, obesity, and history of musculoskeletal disorders) for Achilles tendon disorders with current use was 1.9 (95% CI, 1.3 - 2.6). The recent use and past use groups had similar relative risks to the no use group. The relative risk with current use increased to 3.2 (95% CI, 2.1 - 4.9) in patients $\geq$ 60 years compared to 0.9 (95% CI, 0.5 - 1.6) in patients < 60 years. In addition, the relative risk increased to 6.2 (95% CI, 3.0 - 12.8) in patients $\geq$ 60 years and concomitantly used corticosteroids with fluoroquinolone therapy. The study findings showed that Achilles tendon disorders associated with fluoroquinolones are relatively rare, however patients $\geq$ 60 years who are taking concurrent corticosteroid therapies maybe at increased risk (Van der Linden et al., *BMJ 2002*).

In an attempt to identify risk factors associated with tendonitis/tendon rupture due to fluoroquinolones, Van der Linden et al reported on the follow-up to 42 spontaneously reported cases of fluoroquinolone-associated tendon disorders in the Netherlands between January 1988 and January 1998. Risk factors most frequently associated with tendon disorders included age>60, oral corticosteroid use and existing joint problems. The cases evaluated showed 71% of patients to be over the age of 60, predominantly male (76%:24%), 90% of patients had Achilles tendon involvement, 26% had history of joint problems (rheumatoid arthritis, osteoarthritis, gout, etc), 76% were taking drugs concomitantly with the fluoroquinolones. The most frequently reported symptoms were pain, edema, redness, warmth, and functional disability. The median latency period between start of fluoroquinolone therapy and appearance of symptoms was 6 days, with 93% of cases having latency periods of less than one month. The fluoroquinolones involved with these cases were ofloxacin, ciprofloxacin, norfloxacin and pefloxacin with an average duration of treatment of 14 days (range 2-81 days) (Van der Linden et al., *Arthritis care & Research* 2001).

Seeger et al conducted a case-control study to analyze the comparative risk of tendon rupture among specific fluoroquinolones and assess various risk factors for fluoroquinolone-associated Achilles tendon rupture. A cohort of patients from the Ingenix Research Database (a health insurance claims database) was included in the study. Cases of Achilles tendon rupture were identified using a medical record-validated

algorithm, and controls were randomly sampled from the person-time at risk of experiencing fluoroquinolone-associated tendon rupture The relative risks for Achilles tendon rupture among persons > 60 years and < 60 years were 1.05 (95% CI: 0.47-2.33) and 1.26 (95% CI: 0.89-1.77), respectively. The relative risk for fluoroquinolone exposure in the 0-30 days preceding the index date was 1.39 (95% CI: 0.78-2.49), and was similar to that for each preceding 30-day window across 6 months. The relative risks of tendon rupture for specific antibiotics are outlined in the following table:

Antimicrobial Agent	RR (95% CI)
Ciprofloxacin	1.38 (0.95-2.01)
Levofloxacin	0.64 (0.29-1.41)
Ofloxacin	1.41 (0.56-3.56)
Azithromycin	1.18 (0.89-1.55)
Combined non-FQ antibiotics	1.24 (1.05-1.46)

The authors determined that the risk of Achilles tendon rupture associated with fluoroquinolone exposure was similar across the class and to the risk associated with non-fluoroquinolone antibiotic exposure. The risk of tendon rupture associated with fluoroquinolones was constant across the 6 months following dispensing and was not apparently increased among elderly patients (Seeger et al., *41st IDSA*).

11. Precautions: Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE.

- Metabolic Disorders

  As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately.

Post-Marketing Surveillance

As in clinical trials, hyperglycemia and hypoglycemia associated with levofloxacin have been reported through the post-marketing spontaneous adverse event reporting system. The majority of these reports occurred in patients with diabetes on concomitant medications for glucose control (insulin, oral hypoglycemic agents), or other medications capable of effects on blood glucose. A review of the United States post-marketing reports (12/96 to 9/30/03) did not reveal any reports regarding the occurrence of hyperosmolar non-ketotic hyperglycemic coma.

- Heart Rate and Rhythm Disorders

  Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, rare cases of torsades de pointes, have been reported in patients taking levofloxacin. These reports generally involve patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, or cardiomyopathy should be avoided.

Iannini et al, in a combined retrospective (n=21) and prospective (n=16) trial, evaluated the ECGs of patients receiving levofloxacin therapy. It is not described what characteristics were used to identify patients retrospectively. Of the patients in the study, 56% of patients had prior heart disease, eight patients (22%) had electrolyte imbalances, and six patients (16%) were receiving medications known to prolong the QT interval or cause torsades de pointes. QTc interval either decreased or was unchanged in 12 patients. In the group of patients demonstrating some degree of QTc prolongation, the mean prolongation was 4.6 msec. One patient (with QT > 500 msec.) was reported to have developed torsades de pointes after amiodarone was added to the existing drug therapy (Iannini et al., 40th *ICAAC* 2000).

Noel et al conducted a 4 period, double blind, randomized, cross-over, active-comparator study to compare the occurrence of QT interval prolongation between levofloxacin, ciprofloxacin, moxifloxacin and placebo. Healthy volunteers (n=48) who had a normal 12-lead ECG, had a heart rate between 50 and 100 beats/min, had no medical history of cardiac disease, and were not taking concomitant medications were given single doses of levofloxacin 1000mg, ciprofloxacin 1500mg, moxifloxacin 800mg and placebo. QT intervals were measured manually at >7 defined times up to 24 hours before and after dosing for each of the 4 treatment periods and were corrected using Bazett's formula (QTc =QT/$\sqrt{RR}$) and Fridericia formula (QTc = QT/$\sqrt[3]{RR}$). The effect of treatment on mean postdose QTc, maximum change and change at Cmax was evaluated.

Increases in QT and QTc interval compared with placebo were consistently greater after moxifloxacin compared with either levofloxacin or ciprofloxacin. Regardless of correction used for QT, moxifloxacin demonstrated a mean postdose change from baseline QTc that was statistically greater than placebo ($p < 0.001$). Levofloxacin and ciprofloxacin demonstrated a postdose change from baseline QTc that was statistically greater than placebo only with the Bazette correction ($p<0.05$). Differences in mean postdose QTc change, maximum QTc change and QTc change at Tmax from baseline for levofloxacin and ciprofloxacin compared to moxifloxacin were significant ($p<0.001$). Differences between levofloxacin and ciprofloxacin were not significant. No cases of torsades de

pointes were reported in the trial. Major study findings are summarized in the table below (Noel et al., Clinical Pharmacol Therapeutics 2003):

Table 1			
	Mean Postdose Change in QTc (Bazett) from Baseline *	**Incidence of subjects with a change in QTc (Bazett) greater than 30ms from baseline**	**Incidence of subjects with defined prolonged QTc (Bazett) postdose****
Levofloxacin 1000 mg	3.53 – 4.88ms	33-38%	4.2%
Ciprofloxacin 1500 mg	2.27-4.93 ms	38-40%	2.1%
Moxifloxacin 800 mg	16.34-17.83	72-81%	12.8%
Placebo	Not Provided	17-26%	6.4%

* Mean postdose change is represented as a range because the mean change varied based on the 5 different baseline QTc values that were calculated.
** Prolonged QTc interval was defined as >450 ms for male subjects and >470 ms for female subjects.

A second similarly designed study (n=48) was conducted to determine the effect of 500, 1000, and 1500 mg single doses of levofloxacin on the QT interval.[4] The effect of the 750 mg dose on the QTc was not studied. The results of mean change in QTc from baseline in the single dose levofloxacin study are presented in Table 2. The mean change in QTc from baseline was only significant for the 1500 mg group compared to placebo. The mean QTc change at Tmax differences were significant for 1000mg and 1500 mg groups compared to placebo (Noel et al., 41st *ICAAC* 2001).

Table 2. Levofloxacin QTc Prolongation from Baseline	
	Mean Change in QTc post-dose
Levofloxacin 500mg	1.36 msec
Levofloxacin 1000 mg	2.81 msec
Levofloxacin 1500 mg	6.89 msec
Placebo	-0.69 msec

Post-Marketing Surveillance

United States post-marketing reporting rates (January 1997-May 2003, approximately 55 million prescriptions) are < 1 case of QT prolongation or torsades de pointes per million prescriptions regardless of relationship to the drug.

Worldwide post-marketing reporting rates (January 1997-May 2003, approximately 300 million prescriptions) are <1 case of QT prolongation or torsades de pointes per million prescriptions regardless of relationship to the drug. These low reporting rates are consistent with the incidence of heart rate and/or rhythm disorders of <1%, which was reported in clinical trials, regardless of relationship to drug therapy.

12. Adverse Effects: Levofloxacin was launched as a therapeutic agent in Japan in 1993 and in the United States in 1997. Since then, more than 300 million patients have been treated with LEVAQUIN. Overall, its safety profile has been extremely favorable, with the total incidence of drug-related adverse reactions in patients during Phase III clinical trials conducted in North America being 6.2%. Among patients receiving LEVAQUIN therapy, 4.3% discontinued use due to adverse experiences. The overall incidence, type, and distribution of adverse events (AE) was similar in patients receiving LEVAQUIN doses of 750 mg once daily compared to patients receiving doses from 250 mg once daily to 500 mg twice daily. In clinical trials, the following events were considered likely to be drug-related in patients receiving LEVAQUIN:

Adverse Reactions	Incidence (%)
Nausea	1.2
Diarrhea	1.0
Vaginitis	0.6
Abdominal Pain	0.4
Insomnia	0.4
Flatulence	0.3
Pruritis	0.3
Dizziness	0.3
Rash	0.3
Dyspepsia	0.2
Genital Moniliasis	0.2
Moniliasis	0.2
Taste Perversion	0.2
Vomiting	0.2
Injection Site Reaction	0.2
Injection Site Inflammation	0.1
Constipation	0.1
Fungal Infection	0.1
Genital Pruritis	0.1
Headache	0.1
Nervousness	0.1
Rash Erythematous	0.1
Urticaria	0.1
Maculo-papular Rash	0.1

13. Drug-Drug interactions:

- *Theophylline*

No significant effects of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline were detected in a clinical study of 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with

theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline related AEs in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made, when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels.

- *Warfarin*

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S-warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Liao et al evaluated the potential for an interaction between warfarin and levofloxacin in a double blind, randomized, two-way crossover study of 15 healthy male volunteers. Each subject received 500 mg of levofloxacin or placebo orally every 12 hours on days 1-9. On day 4, a single 30 mg oral dose of warfarin sodium was administered. A 21-day washout period was allowed between the warfarin doses for the two crossover treatments. Blood samples were collected for 144 hours following the warfarin dose for the determination of warfarin plasma concentrations and plasma prothrombin time (PT). There was no statistically significant difference between the two treatments for any of the parameters. Mean baseline PT values were 11.6+/-0.4 and 11.8+/-0.4 sec for placebo and levofloxacin, respectively. Following warfarin administration, the mean PT increased to reach peak of approximately 15 sec by 36 hours in most cases and returned to baseline values for both groups. There was no statistically significant difference between the PT values for the two treatment groups (Liao et al, *J Clin Pharmacol* 1996).

Yamreudeewong et al examined the effect of levofloxacin on INR values in patients stabilized on long-term warfarin therapy. This was a prospective analysis, where 18 patients (average age = 68.0 years ± 8.7) stabilized on warfarin therapy (defined as dosages that maintained INR within the target range for at least 3 weeks) were administered levofloxacin 250-500 mg/day for the treatment of various types of infections based on clinical judgment and diagnoses. Warfarin dosage ranged from 1.5-10 mg/day and the duration of levofloxacin therapy ranged from 5-10 days. The time between the start of levofloxacin therapy and measurement of the first INR was 5 ± 1.29 days (median ± SD). During the study, warfarin dosage adjustments were made in 9 patients, of which 4 required dose decreases and 3 required dose increases, as per the guidelines for their therapeutic INR values. No serious adverse effects (such as serious bleeding complications) were observed in any of the patients during the study. No significant difference was noted between mean INR values obtained before and after

levofloxacin therapy (2.61 ± 0.44 vs. 2.74 ± 0.83, 95% CI: –0.449 to 0.196, p=0.419) (Yamreudeewong et al., *Pharmacotherapy* 2003).

- *Cyclosporine*

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other distribution parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C max and k e were slightly lower, while T max and t ½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

- *Digoxin*

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levolfoxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment is required for levofloxacin or digoxin when administered concomitantly.

- *Probenecid and Cimetidine*

No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $T_{1/2}$ of levofloxacin were 27% – 38% and 30% higher, respectively, while CL/F and CL R were 21% – 35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

- *Non-Steroidal Anti-Inflammatory Drugs*

The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

- *Antidiabetic Agents*

Disturbances of blood glucose levels, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

14. Drug-Food interactions:

- *Antacids, Metal Cations, Sucralfate and Food*

Lee et al. and Guay reported that although the chelation by divalent cations is less marked than that seen with other quinolones, concurrent administration of levofloxacin with antacids containing magnesium or aluminum, as well as sucralfate, metal cations (such as iron), and multivitamin preparations with zinc, may interfere with its gastrointestinal absorption. This could result in systemic levels of levofloxacin that are considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration (Lee et al., *Antimicrob Agents Chemother* 1997; Guay et al., *Drug Interactions in Infectious Diseases* 2000)

Lee et al. reported a study that investigated the effects of food and sucralfate on the pharmacokinetics of levofloxacin after a single, oral 500-mg dose. This was a randomized, three-way crossover study in young, healthy subjects (12 males and 12 females). Levofloxacin was given under three conditions: fasting, fed, and fasting with sucralfate given two hours after levofloxacin. C max , T max , AUC, t 1/2 , CL/F, and CL R were estimated. Both genders were pooled to assess the treatment effect, since there was no significant difference between them. Sucralfate did not alter levofloxacin pharmacokinetics (Lee et al., *Antimicrob Agents Chemother* 1997).

Statistical results indicated that C max and AUC were within the 80%–125% confidence limits between fasting and fed, and between fasting and sucralfate given two hours after levofloxacin. Significant differences were found in T max between fasting and fed, but not between fasting and sucralfate treatment. The mean CL/F and CL R values were similar among all three treatments.

In summary, food did not affect the extent of absorption of levofloxacin, but it did delay the time to maximum plasma concentration. Sucralfate given two hours after levofloxacin did not affect the rate or extent of absorption and should therefore be taken at least two hours before or two hours after levofloxacin.

Videx® (Didanosine) chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. This agent should be taken at least two hours before or two hours after levofloxacin administration.

15. Availability:

Levofloxacin Tablets:

- Tablets are supplied as 250, 500, and 750 mg modified rectangular, film-coated tablets. Levofloxacin tablets should be stored at 15° C to 30° C (50° to 86° F) in well-closed containers.

Levofloxacin Injection:

- Single-Use Vials: Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 ml vials and 750 mg of levofloxacin in 30 ml vials. Levofloxacin injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

- Premix in Flexible Containers: Each bag contains a dilute solution with the equivalent of 250, 500, 750 mg of levofloxacin, respectively, in 5% Dextrose (D_5W). Levofloxacin injection Premix in Flexible Containers should be stored at or below 25° C (77° F); however, brief exposure up to 40° C (104° F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light.

16. Dosing and Administration: Levofloxacin injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOID. Levofloxacin injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage.

Single-use vials require dilution prior to administration.

The usual dose of levofloxacin tablets/injection is 250 mg or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing table. A table below assumes a normal renal function (i.e., creatinine clearance >80 ml/min).

- **Patients with Normal Renal Function**

Infection	Unit Dose	Frequency	Duration
Acute bacterial exacerbation of chronic bronchitis	500 mg	once-a-day	7 days
Nosocomial pneumonia	750 mg	once-a-day	7-14 days
Community acquired pneumonia	500 mg	once-a-day	7-14 days
Community acquired pneumonia	750 mg***	once-a-day	5 days
Acute maxillary sinusitis	500 mg	once-a-day	10-14 days
Complicated skin and skin structure infections	750 mg	once-a-day	7-14 days
Uncomplicated skin and skin structure infections	500 mg	once-a-day	7-10 days
Chronic bacterial prostatitis	500 mg	once-a-day	28 days
Complicated urinary tract infections	250 mg	once-a-day	10 days
Acute pyelonephritis (mild to moderate)	250 mg	once-a-day	10 days
Uncomplicated urinary tract infections (mild to moderate)	250 mg	once-a-day	3 days

***Efficacy of this alternative regimen has been demonstrated to be effective for infections caused by *Streptococcus pneumoniae* (excluding MDRSP), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

- **Patients with Impaired Renal Function**

Renal Status	Initial Dose	Subsequent Doses
ABECB / CAP / Sinusitis / Uncomplicated SSSI / Chronic Bacterial Prostatitis		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI/Nosocomial Pneumonia/ CAP		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI / Acute Pyelonephritis		
$CL_{CR} \geq 20$ mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

ABECB=Acute Bacterial Exacerbation of Chronic Bronchitis, CAP=Community Acquired Pneumonia, Sinusitis=Acute Maxillary Sinusitis, SSSI=Skin and Skin Structure Infections, CL_{CR}=creatinine clearance, CAPD=chronic ambulatory peritoneal dialysis, UTI=Urinary Tract Infections

Co-Prescribed/Concomitant Therapy: In nosocomial pneumonia, where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

3. DISEASE STATE OVERVIEW/SUPPORTING CLINICAL DATA

A. RESPIRATORY TRACT INFECTIONS

a. Acute Bacterial Exacerbations of Chronic Bronchitis

Burden of Disease

- In 2000, COPD was the fourth leading cause of death in the United States with an estimated 122,009 deaths, up to 100,000 of which may be attributable to acute exacerbations of chronic bronchitis (Minino et al 2002).
- In 1996, approximately 89% of the reported cases of COPD were attributable to chronic bronchitis (14 million) (Adams et al 1999).
- Twenty to 60% of the patients with acute respiratory failure secondary to an acute exacerbation require mechanical ventilation, resulting in hospital mortality rates of 20 to 30% (Grossman et al 1997).
- On average a patient with chronic bronchitis experiences one to four acute exacerbations per year with symptoms lasting about 14 days per episode (Saint et al 2001).
- Adams et al (1999) estimated that people sought medical treatment for 90.7% of their acute bronchitis attacks in 1996.
- Neiderman et al (1999), using Medicare claims and the Healthcare Cost and Utilization Project (HCUP) data base estimated a total of 280,839 hospitalizations for acute exacerbations of chronic bronchitis in 1994 resulting in hospital costs of $1.1 billion; and

Etiology

- Bacteria most commonly isolated from sputum in cases of acute bacterial exacerbations of chronic bronchitis were *Haemophilus influenzae* (37%), *Moraxella catarrhalis* (26%), or *Streptococcus pneumoniae* (17%) (Pfaller et al 2002).
- Other bacteria including *S. aureus, Enterobacteriaceae, Pseudomonas aeruginosa*, and *Actinobacter* spp. accounted for 20% of acute bacterial exacerbations of chronic bronchitis. (Pfaller et al 2002).
- In North America and Europe, β-lactamase-mediated amoxicillin resistance can be expected in 20-40% of *H. Influenzae* strains and in almost 100% of *M. catarrhalis* strains (Grossman et al 1997).

Clinical Presentation (In presence of chronic bronchitis)

- Acute exacerbations of chronic obstructive lung disease are characterized by the presence of episodic respiratory decompensation independent of pneumonia (Grossman et al 1997).

- Chronic bronchitis is defined as the 'daily production of sputum for at least three consecutive months in two or more consecutive years.' (American Thoracic Society 1995)
- Acute exacerbations of chronic bronchitis are defined as a worsening of symptoms including an increase in cough, sputum production, purulence, and dyspnea (Adams et al 2000).
- Bacteria were isolated from sputum in 40 to 60% of cases of acute exacerbations of chronic bronchitis (Sethi 2000).
- Isolation of a new strain of a bacterial pathogen at a COPD clinic visit was associated with a significantly increased risk of an exacerbation, supporting the causative role of bacteria in exacerbations of COPD (Sethi et al 2002).

Place of Product in Therapy

- Levofloxacin 500 mg QD has been demonstrated to be effective against the primary clinically relevant pathogens (*H. Influenzae, S. pneumoniae*, and *M. catarrhalis*) and was also shown to be safe and well tolerated in patients with ABECB.
- Levofloxacin is indicated for the treatment of ABECB due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis.*

- **Noncomparative Data:**

Masterton et al conducted a randomized, double blind, multi-center study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis (AECB). Five hundred and thirty-two patients were randomized to receive either levofloxacin 500 mg once daily for 5- or 7-days. The primary efficacy analysis was the clinical response at 7-10 days post-treatment in the per-protocol (PP) population. Sputum samples were obtained prior to receiving study medication as well as at post-treatment and follow-up visits for pathogen isolation, identification, sensitivity testing and assessment of eradication. All patients who received at least one dose of the study medication were evaluated for safety. Clinical success rates in the primary PP efficacy analysis at post-treatment were 83% for the 5-day and 85% for the 7-day group. The difference in success rates was –2.1% with a 95% CI of (-9.1 to 4.9%). Both treatment regimens were well tolerated. The most frequently reported adverse events were diarrhea, headache, nausea and vomiting (Masterton et al., Int J Antimicrob Agents 2001).

- **Comparative Data:**

Levofloxacin vs. Moxifloxacin

A prospective, double-blind, randomized, Phase III trial that enrolled 598 patients was conducted to compare a short-course (5-day) regimen of oral moxifloxacin 400 mg to a 7-day regimen of oral levofloxacin 500 mg for the treatment of acute exacerbation of chronic bronchitis of suspected bacterial origin. Eligible patients were categorized into clinically valid, microbiologically valid, and intent-to-treat populations. Clinical resolution

rate was determined based on the result of clinical assessment at the test-of-cure visit (post-therapy, days 7 to 21) and at follow-up visit (post-therapy, days 27 to 38). Bacteriological response was evaluated based on the results of cultures obtained at the pre- and post-therapy visits. The result of clinical response rates at the test-of-cure and follow-up visits for are presented as follows:

	Clinically-Valid Population	Intent-to-Treat Population
Levofloxacin		
• Test-of-Cure	• 94%	• 95%
• Follow-Up	• 90%	• 89%
Moxifloxacin		
• Test-of-Cure	• 93%	• 92%
• Follow-Up	• 89%	• 87%

A total of 403 pathogens (27% *H. Influenzae*, 13% *M. catarrhalis* and 9% *S. pneumoniae*) were isolated from 594 intent-to-treat patients, whereas 334 bacterial organisms were isolated from 260 microbiologically valid population at the pre-therapy visit. The bacteriological eradication/presumed eradication rates for the microbiologically valid population were 96% for both levofloxacin and moxifloxacin. Total causative pathogen eradication rates at the test-of-cure visit were 97% for both treatment arms. The percents of drug-related events reported were comparable in the levofloxacin and moxifloxacin treatment groups (25% vs. 24%, respectively). The authors concluded that both study medications were well tolerated (Hautamaki et al., 2001).

Levofloxacin vs. Gatifloxacin

Ramirez et al presented a review from the results of three clinical trials conducted in patients with acute exacerbations of chronic bronchitis. One of the multicenter, double-blind, randomized trials compared bacteriologic eradication rates of gatifloxacin 400 mg daily (n = 558; total from three studies) to levofloxacin 500 mg daily (n=179) for 7 to 10 days. Of the patients enrolled in the levofloxacin arm, a pathogen was isolated in 65% of study subjects and 62% in the gatifloxacin group. The bacteria that were most commonly isolated include *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae.* Out of all the pathogens isolated from the patients who received treatment, 98% were susceptible to gatifloxacin and levofloxacin. No statistical difference in microbiologic eradication rates was found between gatifloxacin (93%) and levofloxacin (94%). The authors failed to be report the clinical cure rate for levofloxacin therefore no comparison can be made. The authors note a higher eradication rate S. pneumonia for gatifloxacin (33/33) vs. levofloxacin [15/17 (88%)]. The most common adverse effects, diarrhea and nausea, were not statistically different between the groups (Ramirez et al., *Journ Resp Dis,* 1999).

Further data specific to the results of the trial directly comparing gatifloxacin and levofloxacin are available on the FDA website (BMS A1420-001). The clinical cure rates for the clinically evaluable population were 92% (139/151) for levofloxacin and 88% (127/145) for gatifloxacin (95% CI: -14.6, 6.2). The clinical cure rates for the microbiologically evaluable patients were 92% (93/101) for levofloxacin and 88%

(94/107) for gatifloxacin (95% CI: -10.7,3.3). In this study, 60 gatifloxacin-treated patients and 50 levofloxacin-treated patients experienced drug-related adverse events. More than half all-adverse events were considered mild and no patients in either group experienced a drug-related serious adverse event (New Drug Application for Tequin®, 2002).

Levofloxacin vs. Cefuroxime axetil

DeAbate et al conducted a randomized, multi-center, open-label trial to compare the efficacy and tolerability of levofloxacin 500mg orally once daily for 5-7 days vs. cefuroxime axetil 250mg orally BID for 10 days in acute bacterial exacerbation of chronic bronchitis. A total of 248 patients received levofloxacin for a mean of 7 days and 244 received cefuroxime axetil for a mean of 10 days. Clinical response was 94.6% (210/222) for levofloxacin vs. 92.6% (212/229) for cefuroxime axetil. Eradication rates were 97.4% for levofloxacin and 94.6% for cefuroxime axetil. Resistance to levofloxacin was found in 2% of isolates; 9% of isolates were resistant to cefuroxime axetil. Both treatments were generally well tolerated with the most common adverse event in both groups affecting the gastrointestinal tract (DeAbate et al., *Respir Care* 1997).

Levofloxacin vs. Cefaclor

Habib et al report on a prospective, non-blinded, multi-center, randomized trial comparing the safety and efficacy of 5 - 7 days of therapy with oral levofloxacin (500 mg once daily) with 7-10 days of therapy with cefaclor (250 mg TID) in the treatment of patients with acute bacterial exacerbations of chronic bronchitis (ABECB). Three hundred and seventy-three patients were randomly assigned to either levofloxacin (187) or cefaclor (186). Three hundred and nine patients were clinically evaluable. In the levofloxacin group, 72.1% were cured and 19.5% improved vs. 64.5% cure and 27.1% improved with cefaclor. One hundred ninety-two patients were microbiologically evaluable. The overall bacteriologic eradication rates by pathogen were 94% and 87% for levofloxacin and cefaclor, respectively. Levofloxacin eradicated 100% of *Haemophilus influenzae*, 95% of *Moraxella catarrhalis*, and 90% of *Streptococcus pneumoniae* vs. 71%, 100%, and 86%, respectively, for cefaclor. Clinical success was observed in 92% of the patients in both groups. Drug-related adverse events were reported in 7% and 5% of patients, respectively, with gastrointestinal adverse events being the most common. According to the authors, these results indicate that once daily dosing of levofloxacin is as effective and well tolerated as TID dosing of cefaclor in the treatment of patients with ABECB (Habib et al., *Infect Dis Clin Pract* 1998).

Levofloxacin vs. Clarithromycin or Cefuroxime axetil

A prospective, open-label, randomized trial was conducted to compare the efficacy and tolerability of levofloxacin 500 mg once daily (n=94), clarithromycin 500 mg twice daily (n=97), and cefuroxime axetil 250 mg twice daily (n=92); each were administered for 10 days with food, in patients with acute bacterial exacerbation of chronic bronchitis. Clinical response evaluations were performed between days 12 and 19 or at the time of treatment discontinuation. Clinical cure or improvement rate for the 262 clinically

evaluable patients were 87.4% for levofloxacin, 87.9% for clarithromycin, and 79.8% for cefuroxime axetil. No statistically significant difference was noted between groups.

Overall, all study medications were well tolerated. The percent of premature discontinuations from treatment due to adverse events was 7.4%, 6.2%, and 8.7% for levofloxacin, clarithromycin, and cefuroxime axetil, respectively; there were no statistical difference between groups. The author concluded that levofloxacin, clarithromycin, and cefuroxime axetil showed comparable clinical cure/improvement rates (Weiss. Clinical Therapeutics 2002).

Levofloxacin vs. Azithromycin

Amsden et al conducted a randomized, double-blind, double-dummy, multicenter study with 1:1 treatment allocation that enrolled 235 patients to compare the efficacy and safety of a standard 5-day course of azithromycin (500 mg on day 1 and 250 mg QD for days 2 to 5) to a 7-day course of levofloxacin (500 mg Q24 hours for 7 days) for the outpatient treatment of patients with ABECB. Clinical and bacteriologic responses were evaluated on day 4 of therapy and on day 24 posttherapy. The overall clinical and bacteriologic responses based on the two assessments in clinically and bacteriologically evaluable patients is presented in the table 1 below. In the levofloxacin treatment group, 22% of patients had positive bacterial culture findings and 27% of patients in the azithromycin treatment group had positive bacterial culture findings. The eradication rates for *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in bacteriologically evaluable patients at the posttherapy visit are described in table 2 below.

Table 1: Overall Clinical and Bacteriologic Response Rates

Clinical Response[a]	**Levofloxacin**	**Azithromycin**
• Day 4 of the therapy	92%	89%
• Day 24 posttherapy[b]	86%	82%
Bacteriologic Response[a,c]	**Levofloxacin**	**Azithromycin**
• Day 4 of the therapy	90%	100%
• Day 24 posttherapy[b]	85%	96%

[a]No significant differences between the two treatment groups.
[b]The day 24 visit was considered to be the primary efficacy end point.
[c]Based on the identified respiratory pathogens from sputum culture.

Table 2: Eradication Rates for Three Respiratory Pathogens

Pathogen	**Levofloxacin**	**Azithromycin**
Haemophilus influenzae	83% (5/6)	93% (14/15)
Moraxella catarrhalis	90% (9/10)	100% (7/7)
Streptococcus pneumoniae	100% (2/2)	100% (1/1)

Overall, both levofloxacin and azithromycin were well tolerated by patients, with 20% and 18% of patients, respectively, reporting mild-to-moderate treatment-related adverse events. The majority of the adverse events that were reported were GI related for both study medications. The authors concluded that both levofloxacin and azithromycin

showed comparable clinical and bacteriologic response rates in patients with ABECB (Amsden et al., CHEST 2003).

b. Nosocomial Pneumonia

Burden of Disease

- Using estimates from the US National Hospital Discharge survey (Hall et al 2002) of 31 million hospital admissions in 2000, there were between 158,530 and 317,060 cases of nosocomial pneumonia in 2000 in the US.
- 83% of episodes of nosocomial pneumonia were associated with mechanical ventilation (Richards et al 2000).
- Studies in mechanically ventilated intensive-care patients have documented that nosocomial pneumonia increased hospital length of stay by 9.2 to 20 days (Jarvis 1996).
- Attributable mortality rates for nosocomial pneumonia (mortality in excess of what would have occurred in the absence of the nosocomial infection) are estimated to range between 6.8% and 43% depending on the severity of the underlying condition, the bacterial cause, and the adequacy of initial antibiotic therapy (Craven et al 1995, Jarvis 1996, Kollef et al 2002).
- Several studies have shown that attributable mortality for nosocomial pneumonia is reduced when first-line therapy is adequate (defined as initial use of antibiotics to which the identified pathogens were susceptible) (Hoffken et al 2002) – for example Kollef et al (1998) estimated an attributable mortality rate of 17.7% with adequate treatment and 42% with inadequate treatment.
- Several studies have also shown that switching from inadequate treatment to adequate treatment after culture results are available is not effective at reducing the attributable mortality rate (Hoffken et al 2002).

Etiology

- Bacteria most commonly isolated from nosocomial pneumonia patients who contracted pneumonia within 5 days of being admitted to the hospital are *Staphylococcus aureus* (both methicillin-susceptible and resistant), *Haemophilus influenza*, and *Streptococcus pneumonia* (American Thoracic Society 1995, Kollef et al 1998, Hoffken et al 2002).
- Bacteria most commonly isolated from nosocomial pneumonia patients who contracted pneumonia more than 5 days after being admitted to the hospital are *Staphylococcus aureus* (most likely methicillin resistant), *Haemophilus influenza*, and *Streptococcus pneumonia* as well as *Pseudomonas aeruginosa* and *Acinetobacter* spp (American Thoracic Society 1995, Kollef et al 1998, Hoffken et al 2002).
- Variability in local hospital microbiologic patterns of bacteria and drug resistance is common and local databases could be maintained to ensure adequate first-line therapy (Hofken et al 2002).

Clinical Presentation (Higgins et al 2001)

- Chest radiographic abnormality that is new, progressive or persistent for more than 24 hours, with evidence of infection.
- Evidence should include at least two of the following:

- Purulent sputum,
- Temperature < 36° C or > 38° C, and
- White cell count <5,000 or ≥ 10, 000/mm^3.

Place of Product in Therapy (Higgins et al 2001, American Thoracic Society 1995)

- The antimicrobial therapy guidelines developed by the American Thoracic Society for the management of nosocomial pneumonia are presented in three tables below.

Patients with mild-to-moderate hospital-acquired (nosocomial) pneumonia, no unusual risk factors, onset any time or patients with severe hospital-acquired pneumonia with early onset*

Core Organisms	Core Antibiotics
Enteric gram-negative bacilli (Non-Pseudomonal) Enterobacter species *Escherichia coli* *Klebsiella* species Proteus species *Serratia marcescens* *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* *Streptococcus pneumoniae*	Cephalosporin Second generation Or Non-Pseudomonal third generation Beta-lactam/beta-lactamase inhibitor combination If allergic to penicillin: **Fluoroquinolone** Or Clindamycin + aztreonam

*Excludes patients with immunosuppression

Patients with mild-to-moderate hospital-acquired pneumonia with risk factors, onset anytime*

Core Organisms Plus:	Core Antibiotics Plus:
Anaerobes (recent abdominal surgery, witnessed aspiration)	Clindamycin or beta-lactam/beta-lactamase inhibitor (alone)
Staphylococcus aureus (coma, head trauma, diabetes mellitus, renal failure)	+/- Vancomycin (until methicillin-resistant *Staphylococcus aureus* is ruled out)
Legionella (high-dose steroids)	Erythromycin +/- rifampin[#]
Pseudomonas aeruginosa (prolonged ICU stay, steroids, antibiotics, structural lung disease)	Treat as severe hospital-acquired pneumonia

*Excludes patients with immunosuppression; [#]Rifampin may be added if Legionella species is documented.

Patients with severe hospital-acquired pneumonia with risk factors, early onset or patients with severe hospital-acquired pneumonia, late onset*

Core Organisms Plus:	Therapy
Pseudomonas aeruginosa	Aminoglycoside or **newer Fluoroquinolone**
Acinetobacter species	**Plus one of the following**: Antipseudomonal penicillin Beta-lactam/beta-lactamase inhibitor Ceftazidime or cefoperazone Imipenem Aztreonam[#]
Consider MRSA	+/- Vancomycin

*Excludes patients with immunosuppression; #Aztreonam efficacy is limited to enteric gram-negative bacilli and should not be used in combination with an aminoglycoside if gram-positive or *Haemophilus influenzae* infections is of concern.

- Levofloxacin is indicated for the treatment of nosocomial pneumonia due to Methicillin-susceptible *Staphylococcus aureus; Pseudomonas aeruginosa; Serratia marcescens; Escherichia coli; Klebsiella pneumoniae; Haemophilus influenzae;* or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.
- Efficacy and safety of levofloxacin have been demonstrated in the clinical trial evaluating levofloxacin for the treatment of nosocomial pneumonia.

- **Comparative Data:**

Levofloxacin ± ceftazidime or an antipseudomonal β-lactam vs. imipenem/cilastatin ± amikacin or an aminoglycoside

A multi-center, randomized, open-label study was conducted to compare the safety and efficacy of levofloxacin with that of imipenem/cilastatin in the treatment of nosocomial pneumonia. Four hundred and thirty-eight subjects were enrolled in the study, of which 220 received levofloxacin 750mg once daily for 7-15 days and 218 received imipenem/cilastatin 500mg-1g intravenously every 6-8 hours for 7-15 days. All subjects were initially started on intravenous therapy. Subjects receiving levofloxacin could be switched to oral after a minimum of 24 hours intravenous administration. Subjects in the imipenem/cilastatin arm could be switched to oral therapy (ciprofloxacin 750mg every 12 hours) after a minimum of 72 hours of intravenous administration. Vancomycin could be added when MRSA was suspected of being a causative pathogen of pneumonia. For infections (confirmed or suspected with *P. aeruginosa*), ceftazidime or an antipseudomonal β-lactam was to be used as adjunctive therapy to levofloxacin and amikacin or an aminoglycoside was to be used as adjunctive therapy to imipenem/cilastatin.

The overall clinical success and microbiological eradication rates for both the intent-to-treat and microbiologically evaluable populations are shown in Table 1 and Table 2, respectively. Clinical success and microbiological eradication rates by pathogen are presented in Table 3. In clinically and microbiologically evaluable patients with documented P. *aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (n=11) or piperacillin/tazobactam (n=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the imipenem/cilastatin arm. Vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the imipenem/cilastatin arm for suspected methicillin-resistant *S. aureus* infection (West et al 2003).

Table 1: Posttherapy Clinical Success Rates (West et al 2003)

	Levofloxacin 750mb qd	Comparator	
Population	**n/N [a,b] (%)**	**N/N (%)**	**95% CI[c]**
ITT	135/204 (66.2)	143/206 (69.4%)	(-6.0, 12.5)
Clinically evaluable	70/118 (59.3)	70/112 (62.5%)	(-9.9, 16.2)
Microbiologically evaluable	54/93 (58.1)	57/94 (60.6)	(-12.0, 17.2)

[a]Denominator total in each analysis population for Clinical Success Rate = Cure+Improved+Failure+Unable to Evaluate
[b]n/N = # responding/population
[c]Two-sided 95% CI around the difference (comparator minus levofloxacin) in clinical success

Table 2: Posttherapy Microbiological Eradication Rates (West et al 2003)

	Levofloxacin 750mg qd	Comparator	
Population	**n/N [a,b] (%)**	**N/N (%)**	**95% CI[c]**
ITT[d]	85/166 (51.2)	82/169 (48.5)	(-13.7, 8.3)
Microbiologically evaluable	62/93 (66.7)	57/94 (60.6)	(-20.3, 8.3)

[a]Denominator total in each analysis population for Microbiologic Eradication Rate=Eradicated+Persisted +Unknown
[b]n/N = # responding/population
[c]Two-sided 95% CI around the difference (comparator minus levofloxacin) in microbiologic eradication rates
[d]Subjects with admission pathogens

Table 3: Clinical Success and Microbiological Eradication Rates by Pathogen (West et al 2003)

		Levofloxacin No. (%) of Patients			Imipenem/cilastatin No. (%) of Patients	
Pathogen	**N**	**Clinical Outcome (cured + improved)**	**Microbiological Outcome (eradicated)[a]**	**N**	**Clinical Outcome (cured + improved)**	**Microbiological Outcome (eradicated)[a]**
MSSA[b]	21	13 (61.9)	14 (66.7)	19	15 (78.9)	13 (68.4)
P. aeuroginosa [c]	17	11 (64.7)	10 (58.8)	17	7 (41.2)	5 (29.4)
H. influenzae	16	10 (62.5)	13 (81.3)	15	11 (73.3)	14 (93.3)
E. coli	12	7 (58.3)	10 (83.3)	11	8 (72.7)	7 (63.6)
K. pneumoniae[d]	11	5 (45.5)	9 (81.8)	7	3 (42.9)	6 (85.7)
S. marcescens	11	7 (63.6)	9 (81.8)	7	3(42.9)	2 (28.6)
MRSA	10	6 (60.0)	5 (50.0)	10	7 (70.0)	7 (70.0)
E aerogenes	7	4 (57.1)	5 (71.4)	7	2 (28.6)	5 (71.4)
E. cloacae	5	2 (40.0)	2 (40.0)	5	3 (60.0)	4 (80.0)
P. mirabilis	5	3 (60.0)	3 (60.0)	4	4 (100.0)	2 (50.0)
K. oxytoca	4	2 (50.0)	3 (75.0)	5	2 (40.0)	4 (80.0)
S. pneumoniae	4	3 (75.0)	3 (75.0)	7	4 (57.1)	5 (71.4)
A. baumannii	2	2 (100)	1 (50)	9	5 (55.6)	7 (77.8)

[a]Includes eradicated and presumed eradicated [b]Methicillin-susceptible S. aures; [c] 15/17 received either ceftazidime or piperacillin/tazobactam in the levofloxacin treatment group and 16/17 received an aminoglycoside in the comparator group; [d]The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study.

Blood cultures were also obtained on admission into the study. Seven patients in the levofloxacin treatment arm and 2 patients in the comparator treatment arm had a blood culture positive for *S. aureus.* The microbiologic eradication rates were 57.1% (4/7) for levofloxacin and 50.0% (1/2) for the comparator, respectively. The clinical response rates (defined as either cure or improvement) were 71.4% (5/7) for levofloxacin and 100% (2/2) for the comparator, respectively (West et al 2003).

The study also evaluated the frequency of superinfections that occurred in both treatment groups. In the intent-to-treat population, 41 patients and 38 patients had superinfections between admission and post-therapy in the levofloxacin and comparator treatment arms, respectively. Fewer superinfections with pseudomonads (*P. aeruginosa and S. maltophilia*) occurred in the levofloxacin treatment group (4/54) versus the comparator arm (16/56).

Overall, there were no unusual or unexpected treatment emergent adverse events. The authors concluded that levofloxacin 750mg administered IV/oral once daily was shown to be as well tolerated and at least as efficacious as imipenem/cilastatin 0.5-1g IV every 6-8 hours (switched to ciprofloxacin 750mg orally twice daily) in the treatment of nosocomial pneumonia.

These data were further analyzed to compare the differences in eradicating *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* along with the frequency of superinfections associated with these organisms[i]. As per protocol, adjunctive therapy was encouraged when *P. aeruginosa* was proven or suspected: ceftazidime or other anti-pseudomonas beta-lactam or an aminoglycoside were to be added to the levofloxacin or imipenem/cilastatin arms, respectively. Out of 438 patients in the intent-to-treat group, 61 patients were isolated with *P. aeruginosa* and 8 patients with *S. maltophilia*. The clinical success and microbiological eradication rates are presented in the following table (Table 4).

Table 4: Clinical Success and Microbiologic Eradication Rates

	Levofloxacin (%)	Comparator (%)
Pseudomonas aeruginosa		
Clinical Success Rate		
Intent-to-Treat	25/34 (73.6)	15/27 (55.5)
Microbiologically Evaluable	11/17 (64.7)	7/17 (41.2)
Microbiological Eradication Rate		
Intent-to-Treat	18/34 (52.9)	9/27 (33.3)
Microbiologically Evaluable	10/17 (58.8)	5/17 (29.4)
Stenotrophomonas maltophilia		
Clinical Success Rate		
Intent-to-Treat	4/5 (80)	2/3 (66.7)
Microbiological Eradication Rate		
Intent-to-Treat	5/5 (100)	2/3 (66.7)
Microbiologically Evaluable	2/2 (100)	2/2 (100)

c. Community Acquired Pneumonia

Burden of Disease

- Community-acquired pneumonia is the 6th leading cause of death in the US and the most common cause of death due to infection (Kuti et al 2002).
- In United States, the overall rates of death due to pneumonia and influenza increased by 59% from 1979 through 1994 (Bartlett et al 2000).
- Estimated to occur in 10 to 12 people per 1000 per year with attack rates higher at the extremes of age (Mandell 1995).
- The US National Health Interview Survey estimated an incidence of 4.8 million cases of pneumonia during 1996 (Adams et al 1999).
- In United States, 2-3 million cases of CAP contribute to about 10 million physician visits, and 500, 000 hospitalizations (Bartlett et al 2000).
- Pneumonia was reported as the cause of 63,548 deaths in the US in 2000 (Minino et al 2002).
- The estimated incidence of CAP requiring hospitalization is reported to be 258 persons per 100,000 population and 962 per 100,000 persons $\geq$ 65 years old (Bartlett et al 2000).
- 54.6 million restricted activity days and 31.5 million bed days were reported for pneumonia in the 1996 US National Health Interview Survey (Adams et al 1999).
- 2.6 million work loss days and 2.6 million school loss days were reported for pneumonia in the 1996 US National Health Interview Survey (Adams et al 1999).
- The mortality rate from pneumonia treated in the outpatient setting is low (< 1%) while mortality rates for those who require hospitalization is14%);and 40% for those requiring admission to the intensive care unit (Kuti et al 2002).
- 90% of pneumonia cases were reported to receive medical care in the 1996 US National Health Interview Survey (Adams et al 1999);
- Niederman et al (1998) estimated a total of 4.5 million visits annually to physicians' offices, emergency departments, and outpatient clinics for CAP in the US.
- 1.38 million discharges from short stay hospitals were reported for pneumonia in the US Hospital Discharge Survey in 1999 with an average length of stay of 6 days (Popovic 1999).
- Average cost per hospital stay were $7,166 for patients aged over 64 years and $6,042 for patients aged under 65 years (Niederman et al 1998);
- Niederman et al (1998) estimate total annual costs of $8.4 billion for health care for CAP; and
- Outpatient costs account for only $384 million of the annual costs for about 80% to 85% of patients who are treated in the outpatient setting (Niederman et al 1998).

Etiology

- Bacteria most commonly isolated from CAP patients are *Streptococcus pneumoniae* (37%), *Haemophilus influenzae* (31%), and *Moraxella catarrhalis* (13%) (Pfaller et al 2002).

- Other implicated pathogens include: *H. influenzae, M. pneumoniae, C. pneumoniae* (5% to 15%)*, S. aureus, S. pyogenes, N. meningitidis, M. catarrhalis, K. pneumoniae* and other gram-negative rods, *Legionella* species (2% to 6%), viruses, and other microbes (Bartlett et al 2000).
- The frequency of the etiologic pathogen is usually dependent on specific epidemiological factors (e.g., alcoholism, COPD/smoking, nursing home residency, etc.)(Bartlett et al 2000).

Clinical Presentation (Bartlett et al 2000).

- Fever or hypothermia
- Rigors
- Sweat
- New cough with or without sputum production
- Change in color of respiratory secretions in a patient with chronic cough
- Chest discomfort
- Fatigue
- Myalgia
- Abdominal pain
- Anorexia
- Headache
- Presence of an acute infiltrate on a chest radiograph
- Altered breath sounds and/or rales

- Onset of dyspnea

Place of Product in Therapy

- In order for an antimicrobial to be effective in the treatment of respiratory tract infections, it must achieve sufficiently high tissue concentrations at the site of infection.
- Levofloxacin rapidly penetrates lung tissue and fluid compartments, with concentrations in lung epithelial lining fluid (ELF) and alveolar macrophages exceeding the MIC_{90} for *S. pneumoniae* and other key respiratory pathogen.
- The 2003 IDSA guidelines recommend the respiratory quinolones as first-line therapy for CAP in hospitalized patients and in outpatients with comorbidities or in outpatients who been received recent antibiotic therapy (Mandell et al. CID 2003)
- The most recent antimicrobial therapy guidelines developed by the Infectious Disease Society of America (IDSA) for the management of CAP in adults are presented in the table below.

IDSA Guidelines **Empirical Therapy Recommendations for CAP** Adapted from Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37:1405-33.	
Outpatients Previously healthy	
• No recent antibiotic therapy	• A macrolide or doxycycline
• Recent antibiotic therapy within past 3 months	• A **respiratory fluoroquinolone** alone or an advanced macrolide plus a β-lactam
Comorbidities (COPD, diabetes, renal failure, CHF, or malignancies)	
• No recent antibiotic therapy	• An advanced macrolide or a **respiratory fluoroquinolone**
• Recent antibiotic therapy within past 3 months	• A **respiratory fluoroquinolone** alone or an advanced macrolide plus a β-lactam
Hospitalized patients General medical ward	
• No recent antibiotic therapy	• A **respiratory fluoroquinolone** alone or an advanced macrolide plus a β-lactam
• Recent antibiotic therapy within past 3 months	• A **respiratory fluoroquinolone** alone or an advanced macrolide plus a β-lactam (regimen selected will depend on nature of recent antibiotic therapy)
Intensive care unit	
• Pseudomonas infection is not an issue	• A β-lactam plus either an advanced macrolide or a **respiratory quinolone**
• Pseudomonas infection is not an issue and β-lactam allergy	• A **respiratory quinolone**, with or without clindamycin
• Pseudomonas infection is an issue	• Either (1) an antipseudomonal agent plus ciprofloxacin or (2) an antipseudomonal agent plus an aminoglycoside plus a **respiratory fluoroquinolone** or a macrolide
• Pseudomonas infection is an issue and β-lactam allergy	• Either (1) aztreonam plus **levofloxacin*** or (2) aztreonam plus moxifloxacin or gatifloxacin, with or without aminoglycoside
Macrolide: erythromycin, azithromycin, clarithromycin. Respiratory fluoroquinolone: **levofloxacin**, gatifloxacin, moxifloxacin, or gemifloxacin. Advanced macrolide: azithromycin or clarithromycin. Oral β-lactam: high dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, cefuroxime. IV β-lactam: cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem. Antipseudomonal agent: piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime. *Dosage for hospitalized patients, 750 mg q.d.	

- Efficacy has been demonstrated in the clinical trials evaluating levofloxacin for the treatment of CAP.
- In a multicenter, double blind, randomized study, levofloxacin 750 mg for five days was found to be as effective and as safe as levofloxacin 500 mg for ten days.
- In comparative trials, levofloxacin clinical and microbiological responses have been equal or superior to traditional regimens.

- Levofloxacin is indicated for the treatment of mild, moderate and severe CAP due to *S. aureus, S. pneumoniae* (including multi-drug resistant strains), *H. influenzae, H. parainfluenzae, K. pneumoniae, M. catarrhalis, C. pneumoniae, L. pneumophila,* or *M. pneumoniae.*

    - **Short-Course Regimen**

Levofloxacin 750 mg for 5 days vs. levofloxacin 500 mg for 10 days

A multicenter, double blind, randomized study was conducted to compare levofloxacin 750 mg QD IV or PO for five days versus levofloxacin 500 mg QD IV or PO for ten days in the treatment of mild to severe CAP in adults (Dunbar, 2003). Diagnosis of mild to severe CAP was based on clinical signs and symptoms of a lower respiratory tract infection and radiographic evidence of acute pneumonia. Randomization included stratification of patients by study center and Pneumonia Severity Index (PSI). Patients with a PSI score of ≤ 70 could be treated as inpatients or outpatients (stratum II) whereas those with a PSI >70 but ≤ 130 were to be treated as inpatients for ≥ 24 hours (stratum I). The prospectively defined primary endpoint was clinical success rate (cured + improved) at the posttherapy visit scheduled to occur 7-14 days after receipt of last active dose.

Overall, a total of 530 patients were randomized. Of the clinically evaluable patients at posttherapy, the clinical success rate was 92.4% (183/198) for the levofloxacin 750 mg group and 91.1% (175/192) for the levofloxacin 500 mg group (95% CI:-7.0, 4.4). Clinical success rates were comparable for levofloxacin 750 mg and levofloxacin 500 mg treatment groups within the two severity strata (90.8% vs. 84.9% for stratum I; 93.4% vs. 96.2% for stratum II). The most common pathogens identified at admission were *S. pneumoniae, H. influenzae*, *H. parainfluenzae. M. pneumoniae, C. pneumoniae, L. pneumophila,* The microbiologic eradication rate for microbiologically evaluable patients at posttherapy was 93.2% (96/103) for the levofloxacin 750 mg group and 92.4% (85/92) for the levofloxacin 500 mg group (95% CI: -8.6,7.0). Microbiologic eradication rates in the microbiologically evaluable population for specific pathogens are found in the table below:

Pathogen	**Levofloxacin 750 mg (n=103)**	**Levofloxacin 500 mg (n=92)**	**95% CI**
H. influenzae	12/13 (92.3%)	12/14 (85.7%)	-33.8 to 20.6
H. parainfluenzae	12/12 (100%)	9/10 (90%)	-33.6 to 13.6
S. pneumoniae	19/22 (86.4%)	17/20 (85%)	-25.1 to 22.4
C. pneumoniae	20/22 (90.9%)	16/16 (100%)	-6.0 to 24.2
L. pneumophila	11/11 (100%)	3/3 (100%)	NA
M. pneumoniae	41/43 (95.3%)	34/36 (94.4%)	-12.1 to 10.3

Symptom resolution was also evaluated in the study. By day 3 of therapy, 67.4% of patients in the 750 mg group reported subjective resolution of fever, compared with 54.6% of patients in the 500 mg group (p=0.006). Similarly, defervescence by day 3 was

achieved in a significantly greater number of patients in the levofloxacin 750 mg group versus the levofloxacin 500 mg group (49.1% vs. 38.5%, p=0.027). The overall safety profile of the 750 mg dose was not significantly different from the 500 mg dose. Nausea (8.6%) and headache (8.6%) were the most common adverse events for the 750 mg group, and insomnia (10.6%) and diarrhea (6.0%) were the most common adverse events for the 500 mg group. The authors concluded that short-course levofloxacin 750 mg was as effective as levofloxacin 500 mg for the standard ten days in the treatment of outpatient and hospitalized patients with CAP.

- **Noncomparative Data:**

Fogarty et al evaluated the safety and efficacy of levofloxacin for the treatment of CAP in 264 adult patients in an open-label, multicenter, noncomparative trial. Patients were treated with levofloxacin 500 mg PO or IV (according to an assessment of severity) QD for 7 to 14 days. The mean duration of therapy was approximately 13 days. The most common pathogens identified were *H. influenzae*, *S. pneumoniae,* and *C. pneumoniae*. Twenty-one patients had a single atypical pathogen and 79 patients had a single typical pathogen. Polymicrobial infections occurred in 38 patients, with approximately 50% of these patients coinfected with both typical and atypical pathogens. Levofloxacin was well tolerated, the most common drug-related adverse events were diarrhea (1.5%) and nausea (1.1%). The authors concluded that regardless of the number of pathogens and the severity of the pneumonia, levofloxacin 500 mg QD, IV or PO, achieved an overall excellent eradication/clinical success rate with minimal side effects. The results are summarized in the table below (Fogarty et al., *Infect Dis Clin Pract* 1998).

SUMMARY OF RESULTS FROM FOGARTY ET AL

	Clinically evaluable N =234	**Microbiologically evaluable N = 136**
Infection severity (%)		
Severe	40(17.1)	34(25)
Mild to moderate	194(82.9)	102(75)
Patient status (%)		
Inpatient	88(37.6)	62(45.6)
Outpatient	146(62.4)	74(54.4)
Route of administration (%)		
IV only (3d)**	2(0.9)	
PO Only (13.3d)**	161(68.8)	
IV/PO (4d, 9d)**	71(30.3)	
Clinical success* rate (%)	222(94.9)	130(95.6)
Eradication rate (%)		129(94.9)

*Clinical success was evaluated 5 to 7 days post-therapy and defined as the sum of cured patients and improved patients.
**mean duration of therapy (in days)

CAP due to Multi-Drug Resistant *Streptococcus pneumoniae*

An analysis of all patients treated with levofloxacin for the treatment of CAP revealed 95% (38/40) clinical and bacteriologic success in 40 microbiologically evaluable patients

with multi-drug resistant S. pneumoniae (MDRSP) isolates. MDRSP isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC value ³ 2 mg/ml), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole. Clinical success rates for levofloxacin were 94.4% (17/18) in patients with S. pneumoniae resistant to two antibiotics, 93.3% (14/15) in patients with S. pneumoniae resistant to three antibiotics, and 100% (7/7) in patients with S. pneumoniae resistant to four antibiotics. In all groups, bacteriologic eradication rates were the same as clinical success rates. Additionally, in patients with bacteremias due to MDRSP, the clinical success rate and bacteriologic eradication rate was 89% (8/9). Thus, based on clinical evidence, LEVAQUIN has excellent efficacy against MDRSP.

CAP due to Penicillin-Resistant *Streptococcus pneumoniae*

To evaluate the safety and efficacy of levofloxacin 500 mg IV or PO QD for 10-14 days in the treatment of CAP and to evaluate its activity against penicillin-susceptible and penicillin-resistant pneumococci, Kahn et al conducted a phase IV, multicenter, noncomparative trial. There were 1095 clinically evaluable patients enrolled in the trial and 188 patients had a culture-proven isolate identified as *S. pneumoniae*. The table below summarizes the data from the clinically evaluable patients with a *S. pneumoniae* isolate vs. penicillin susceptibility. The authors concluded that levofloxacin is highly effective when used for the treatment of CAP and is active against most common respiratory pathogens, including penicillin-resistant *S. pneumoniae* (Kahn et al., 38th *IDSA* 2000).

CLINICALLY EVALUABLE PATIENTS WITH IDENTIFIED S*. PNEUMONIAE* ISOLATES

	Clinical Success	**Microbiologically eradicated**
Penicillin-susceptible, N = 115 (%),	106(92)	106(92)
Penicillin-Intermediate, N = 17 (%)	17(100)	17(100)
Penicillin-resistant, N = 5 (%)	5(100)	5(100)
Penicillin-susceptibility unknown, N = 47 (%)	47(92)	47(92)
Total *S. pneumoniae* isolates, N = 188 (%)	175(93)	175(93)

Levofloxacin was the first antimicrobial to receive an indication for the treatment of CAP due to penicillin-resistant *S. pneumonia*e. A review of eight clinical trials in which levofloxacin efficacy was evaluated for treatment of CAP identified 513 patients with microbiologically proven pneumococcal infections treated with levofloxacin since 1993.

Of these, 253 patients were clinically and microbiologically evaluable. Fifty-nine (23.3%) of the 253 patients were infected with isolates having reduced penicillin susceptibility, and 15 (5.9%) exhibited high-level penicillin resistance (MIC³2 µg/mL). Only one of the isolates tested was resistant to levofloxacin (MIC=16 µg/mL). Clinical cure and microbiological eradication rates were both 100% for the patients infected with penicillin-resistant (MIC³ 2 µg/mL) or -intermediate (MIC 0.1–1.0 µg/mL) isolates, including one levofloxacin-resistant pathogen (MIC=16 µg/mL).

In these analyses, penicillin susceptibility, severity of infection, bacteremic status, and age of the patient had no effect on clinical success or microbiologic eradication (table).

Clinical success was 97% for severely ill patients as determined by clinical criteria, and 100% for the 55 severely ill patients with pneumococcal bacteremia.

Clinical and Microbiological Responses for Levofloxacin-treated CAP Patients from Different Risk Groups					
		Clinical Outcome		Microbiologic Outcome	
Subject Category*	**N**	**Success (%)**	**Failure**	**Eradicated(%)**	**Persisted**
Severe	100	97 (97)	3	97 (97)	0
Bacteremic	55	55 (100)	0	55 (100)	0
Penicillin-resistant	15	12 (100)	0	12 (100)	0
Age ≥ 65	86	83 (97)	3	84 (98)	2
*Patients were included in multiple categories when applicable.					

CAP Due to *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*

File and colleagues reported a 98% clinical success rate for patients treated with levofloxacin for documented *C. pneumoniae* infections; the rate was 100% for those infected with *L. pneumophila* or *M. pneumoniae*. Overall, the clinical success rates for *C. pneumoniae*, *M. pneumoniae*, and *L. Pneumophila* are 96%, 96%, and 70%, respectively (File et al., *Antimicrob Agents Chemother* 1997).

Williams et al. enrolled 655 patients in a noncomparative study of the efficacy and safety of levofloxacin (500 mg IV/PO qd) in the treatment of CAP. Twenty-six patients (4.0%) fulfilled predetermined criteria for the diagnosis of CAP due to *L. pneumophila*. The most common copathogens were *M. pneumoniae* (7), *S. pneumoniae* (6), and *C. pneumoniae*. The clinical success with levofloxacin treatment was 92% (24/26). The mean duration of treatment was 12.04 ± 2.8 days (range, 7–14 days). Only one AE (3%) was considered probably or definitely related to study drug administration (IV-site phlebitis) (Williams et al., 36th *IDSA* 1998).

In a subsequent report from the same trial, patients had CAP due to *M. pneumoniae* and 32 patients had CAP due to *C. pneumoniae*. Ninety and 28 of these patients, respectively, were clinically evaluable at a post-therapy visit. Levofloxacin treatment exhibited clinical success in 89/90 (98.9%) of the *M. pneumoniae* cases and 27/28 (96.4%) of the *C. pneumoniae* cases (table).

Levofloxacin Clinical Response by Pathogen in Clinically Evaluable Patients				
Pathogen	**N**	**Cured (%)**	**Improved (%)**	**Failed (%)**
C. pneumoniae	28	15 (53.6)	12 (42.9)	1 (3.6)
M. pneumoniae	90	64 (71.1)	25 (27.8)	1 (1.1)
L. pneumophila	26	19 (73.1)	5 (19.2)	2 (7.7)

- **Comparative Data:**

Levofloxacin vs. Ceftriaxone ± Cefuroxime axetil

A study by File et al demonstrated that clinical outcomes with levofloxacin were significantly better than with a cephalosporin regimen for empirical treatment of CAP. This study was a prospective, multicenter, randomized, open-label study comparing the safety and efficacy of 7 to 14 days of levofloxacin treatment with that of ceftriaxone and/or cefuroxime axetil in 590 adult patients with CAP. Patients were randomized (1:1) to receive either levofloxacin (IV and/or PO) 500 mg QD or ceftriaxone (IV) 1 or 2 g QD or BID and/or cefuroxime axetil (PO) 500 mg BID and could be treated either in the hospital or on an outpatient basis. For those patients receiving a cephalosporin, erythromycin could be added at the discretion of the investigator for atypical organism coverage. The mean total duration of therapy for both treatment groups was 11.7 days. The most common typical bacterial pathogens among clinically evaluable patients were *S. pneumoniae* (isolated from 63 sputum specimens) and *H.influenzae* (isolated from 54 sputum specimens). One hundred atypical pathogens were identified. The results are summarized in the table below. Drug-related adverse events were reported in 5.8% of patients receiving levofloxacin and 8.5% of patients administered ceftriaxone and/or cefuroxime (File et al., *Antimicrob Agents Chemother* 1997).

SUMMARY OF RESULTS FROM FILE ET AL

	Levofloxacin N = 295		**Ceftriaxone and/or cefuroxime axetil N = 295**	
	Clinically evaluable N =226	Microbiologically evaluable N = 128	Clinically evaluable N = 230	Microbiologically evaluable N = 144
Infection severity (%)				
Severe	36(16)	21(16)	37(16)	28(19)
Mild to moderate	190(84)	107(84)	193(84)	116(81)
Patient status (%)				
Inpatient	104(46)	60(47)	96(42)	60(42)
Outpatient	122(54)	68(53)	134(58)	84(58)
Mortality of inpatient patients (%)	1.4%		5.6%	
Route of administration (%)				
IV only	5(2.2)		5(2.2)	
PO Only	138(61)		116(50.4)	
IV/PO	83(36.8)		109(47.4)	
Clinical success* rate (%)	217(96)		207(90)	
Eradication rate (%)		125(98)		122(85)

*Clinical success was evaluated 5 to 7 days post-therapy and defined as the sum of cured patients and improved patients.

Levofloxacin vs. Azithromycin + Short-course (2 day) Ceftriaxone

In a phase IV, multicenter, open-label study by Kahn et al, the efficacy of levofloxacin monotherapy was compared to azithromycin (+ ceftriaxone for the first 2 treatment days) therapy in adults with moderate to severe pneumonia (Fine risk score, 60 to 140). Patients were randomized to receive at least a 10-day course of therapy with either levofloxacin 500 mg IV or PO QD or azithromycin 500 mg IV + ceftriaxone 1g IV QD (for a minimum of 2 days) followed by azithromycin 500 mg IV or PO QD. The authors concluded that levofloxacin monotherapy is safe and effective for patients with moderate-to-severe CAP and clinical and microbiologic outcome with levofloxacin is

comparable to treatment with azithromycin/ceftriaxone. Levofloxacin was better tolerated, with fewer emergent adverse events and fewer treatment-emergent serious adverse events, than azithromycin/ceftriaxone. The table below summarizes the study's findings (Kahn et al., 37th *IDSA* 1999).

SUMMARY OF RESULTS FROM KAHN ET AL

	Levofloxacin N = 115		**Azithromycin and/or ceftriaxone N = 121**	
	Clinically evaluable N = 85	Microbiologically evaluable N = 36	Clinically evaluable N = 78	Microbiologically evaluable N = 35
Clinical success* rate (%)	80(94.1)	33(91.7)	72(92.3)	33(94.3)
Eradication rate (%)		33(91.7)		33(94.3)

*Clinical success was evaluated 2 to 7 days post-therapy and defined as the sum of cured patients and improved patients.

Levofloxacin vs. Gatifloxacin

Sullivan et al conducted a randomized, double-blind clinical trial evaluating the safety and efficacy of gatifloxacin 400 mg QD vs. levofloxacin 500 mg QD for the treatment of community-acquired pneumonia in 417 patients. More than 50% of the patient population studied in this clinical trial had one or more co-morbid pulmonary diseases (bronchitis, COPD, emphysema, etc.). The most common pathogens identified were *H. parainfluenzae* (n = 30 for gatifloxacin, n = 16 for levofloxacin), *S. aureus* (n = 29 vs. n = 17), *S. pneumoniae* (n = 17 vs. n = 18), *H. influenzae* (n = 12 vs. n = 13), *M. catarrhalis* (n = 13, vs. n = 8) and atypical organisms (n = 17 vs. n = 17). The clinical cure rates were 96% and 94% for gatifloxacin and levofloxacin, respectively. The authors concluded that levofloxacin and gatifloxacin demonstrated comparable efficacy in the empiric treatment of CAP (Sullivan et al., *J Resp Dis* 1999).

An analysis of the same study revealed slightly different results (BMS A1420-038). Clinical cure rates for the clinically evaluable population were 93% (166/178) for levofloxacin and 90% (154/172) for gatifloxacin (95% CI: -11.5,3.6). Clinical cure rates for the microbiologically evaluable population were 95% (77/81) for levofloxacin and 91% (83/91) for gatifloxacin (95% CI: -15.3,6.9). A safety analysis revealed that 58 gatifloxacin-treated patients and 32 levofloxacin-treated patients experienced drug-related adverse events. The majority of all adverse events was considered mild or moderate and were most commonly nausea, diarrhea, constipation, vomiting, vaginitis, and dizziness. Additionally, two gatifloxacin-treated patients and no levofloxacin-treated patients were reported to have a drug-related serious adverse event. These events were bradycardia and diabetes (New Drug Application for Tequin®).

Levofloxacin vs. Moxifloxacin

File et al (*Today's Ther* Trends, 2001) conducted a prospective, randomized, double-blind, double-dummy, Phase III study that enrolled 516 patients to compare the efficacy and safety of sequential IV/PO moxifloxacin 400mg/400mg once daily (n=253) to an IV alatrofloxacin/PO trovafloxacin 200mg/200mg once daily (n=263) for the treatment of

CAP in hospitalized patients requiring initial IV therapy. During the study, the original comparator, IV alatrofloxacin/PO trovafloxacin 200mg/200mg once daily was changed to IV/PO levofloxacin 500mg/500mg once daily due to the potential for trovafloxacin-related hepatotoxicity. All patients received IV antibiotic for a minimum of three days and then switched to the assigned oral antibiotic for a total of 7-14 days. Clinical success was determined at the test-of-cure visit (7-30 days post-therapy). Additionally, 12-lead ECG monitoring was performed at pre-therapy (within 2 hours) and post therapy (end of infusion) on Day 1 and Day 3 to evaluate the cardiac safety profile of study drugs. The clinical response rates are presented in Table 1. The FDA subset analysis result that compared moxifloxacin and levofloxacin-phase of the study is presented in Tables 2 and 3.

Table 1. Moxifloxacin versus Comparators (Alatrofloxacin/Trovafloxacin and Levofloxacin combined data)

Population	Moxifloxacin	Comparators	95% CI
Clinically-valid	88% (155/177)	89% (160/179)	(-7.3%, 5.6%)
• Mild/moderate	92% (107/116)	93% (121/130)	
• Severe	79% (48/61)	80% (39/49)	
Microbiologically-valid	85% (64/75)	90% (69/77)	(-16.1 %, 7.6%)

Table 2. FDA Subset Sensitivity Analysis using all Moxifloxacin data versus Levofloxacin-phase only (New Drug Application for Avelox®)

Stratum	Moxifloxacin	Levofloxacin	95% CI
All strata	86% (157/182)	89.8% (115/128)	(-10.8%, 27%)
Mild/moderate	90% (109/121)	92% (85/92)	(-9.9%, 5.3%)
Severe	78.7% (48/61)	86% (30/36)	(-20.6%, 11.3%)

Table 3. FDA Subset Sensitivity Analysis of Moxifloxacin data during Levofloxacin-phase only

Stratum	Moxifloxacin	Levofloxacin	95% CI
All strata	87.2% (109/125)	90.6% (115/127)	(-9.4%, 5.4%)
Mild/moderate	95% (75/79)	92% (85/92)	(-4.7%, 9.8%)
Severe	74% (34/46)	86% (30/35)	(-29.0%, 5.4%)

The investigators reported drug-related adverse events were 39% for moxifloxacin and 40% for comparators (alatrofloxacin/trovafloxacin and levofloxacin combined data). The change in QT interval from pre-treatment baseline was 3 ± 28 msec for moxifloxacin and -4 ± 25 msec for comparators (alatrofloxacin/trovafloxacin and levofloxacin combined data). QT prolongation-related cardiovascular morbidity or mortality was not reported in either treatment groups. The authors concluded that clinical success rates and occurrence of adverse events were similar in both treatment groups.

Levofloxacin vs. Amoxicillin/Clavulanate

A randomized, double blind, prospective clinical trial by Carbon et al compared levofloxacin 500 mg QD, levofloxacin 500-mg BID, and amoxicillin/clavulanate 625-mg three times a day in community acquired pneumonia. The authors concluded that levofloxacin, as a single 500-mg daily dose was as clinically and bacteriologically effective as a 500-mg twice-daily dosing regimen (Carbon et al., *Clin Microbiol Infect* 1999).

Levofloxacin vs. Clarithromycin

Gotfried et al conducted a double blind, randomized, multi-center study in ambulatory patients with community-acquired pneumonia. Patients were randomized to receive either clarithromycin extended-release (ER) 2x500 mg once-daily (n=156) or levofloxacin 2x250 mg once daily (n=143) for 7 days. Primary efficacy evaluations were Test-of-Cure at 14-21 days after the last dose of treatment. Results demonstrated no statistically significant differences between clarithromycin ER and levofloxacin groups in the clinical cure rate, overall or individual pathogen eradication rates and radiographic success rates (results shown in table).

SUMMARY OF RESULTS FROM PALMER ET AL

	Clarithromycin ER	**Levofloxacin**
Clinical cure rate*	88% (113/128)	86% (107/124)
Bacteriological cure rate**	86% (80/93)	88% (85/97)
Overall pathogen eradication rate**	87% (134/154)	88% (136/155)
Radiographic success rate*	95% (117/123)	88% (104/118)

*clinically evaluable or **clinically and bacteriological evaluable population

The incidences of common adverse events (diarrhea, headache, and nausea) were similar for clarithromycin ER and levofloxacin, while altered taste was significantly higher for clarithromycin ER (Gotfried et al., *Clinical Therapeutics* 2002).

A phase IV, multicenter, open-label, randomized, comparative trial by Kahn et al examined the efficacy and safety of levofloxacin monotherapy versus combination therapy with ceftriaxone sodium and erythromycin, followed by amoxicillin/clavulanate and clarithromycin, in the treatment of CAP patients with higher probability of death than reported in the course of many previously published trials. The inclusion criteria was as follows: 1) hospitalization required, 2) diagnosis of severe CAP (≥3 ATS criteria for hospital admission, 3) need for mechanical ventilation or ≥ 2 of the following (oral temp ≥38°C or ≤35.5°C, respiratory rate ≥30/min, pulse rate ≥130/min, systolic BP <90 mm Hg, altered mental state, 4) infection acquired in community/nursing home, 5) venous access, 6) previous antimicrobials taken for <24 hours or taken ≥ 72 hours and patient classified as a treatment failure. Two-hundred and sixty-nine patients were randomized to 1 of 2 treatment regimens: 1) levofloxacin 500 mg IV q24h for ≥ 1 day, followed by levofloxacin 500 mg PO q24h, for a total of 7-14 days (132 patients), 2) ceftriaxone sodium 1 to 2 grams IV or IM q24h + erythromycin 500-1000 mg IV q6h, followed by amoxicillin/clavulanate 875 mg PO q12h + clarithromycin 500 mg PO q12h for a total of 7-14 days (137 patients). Levofloxacin was well tolerated, with a safety profile at least equivalent to that of the comparator. The authors concluded that levofloxacin

monotherapy is effective when used for the treatment of seriously ill patients with CAP at high risk of dying. The table below summarizes the results of the study (Kahn et al., *CHEST* 2000).

SUMMARY OF RESULTS FROM KAHN ET AL

	Levofloxacin monotherapy N = 132		**Comparator N = 137**	
	Clinically evaluable N = 95	Microbiologically evaluable N = 53	Clinically evaluable N = 89	Microbiologically evaluable N = 64
Mean APACHE score (SD±)	16.0 ± 5.82		16.5 ± 6.65	
Clinical success* rate (%)	85/95 (89.5)	48/53 (90.6)	74/89 (83.1)	53/64 (82.8)
Eradication rate (%)	45/55 (81.8)	45/53 (84.9)	48/65 (73.8)	48/64 (75.0)

*Clinical success was evaluated 3 to 12 days post-therapy and defined as the sum of cured patients and improved patients.

d. Acute Maxillary Sinusitis

Burden of Disease

- More than 30 million individuals are affected with sinusitis each year in the United States (Brook et al 2000).
- Annually, approximately 16% of adults are diagnosed with sinusitis in the United States (Brook et al 2000).
- Accounts for about 90% of primary care physician visits (Brook et al 2000).
- In 1995 non-federally employed physicians in office based practices saw 3 million cases of acute sinusitis – total physician office visits for acute and chronic sinusitis were 11.6 million in 1991 (McCaig et al 1995);
- In 1993, there were 16,000 hospital discharges for acute sinusitis and a total of 45,000 hospital discharges for both acute and chronic sinusitis (Hahn et al 1994).
- Pei (2000) estimated the average cost of an episode of acute sinusitis as $648.
- Approximately $16 million is spent on office visits per year (Brook et al 2000).
- More than $2 billion is spent annually for over-the-counter medications (Brook et al 2000).
- Expenditures attributable to acute bacterial sinusitis total approximately $3.5 billion annually in the US (Sinus and Allergy Health Partnership, 2004).
- In 2002, approximately $400 to $600 million was spent on antibiotic prescriptions for acute sinusitis (Sinus and Allergy Health Partnership, 2004).
- 16.9 million work loss days and 82 million restricted activity days for acute upper respiratory tract infections other than the common cold were reported in the National Health Interview Survey in 1996 (Adams et al 1999).

Etiology

- Bacteria most commonly isolated from adult acute sinusitis patients are *Streptococcus pneumoniae* (20% to 43%%) *Haemophilus influenzae* (22% to 35%%), and *Moraxella catarrhalis* (2% to 10%%) (Sinus and Allergy Health Partnership, 2004).
- Other bacteria including *Staphylococcus aureus* and anaerobes are found in 0% to 8%, and 4% of sinusitis patients, respectively (Sinus and Allergy Health Partnership, 2004).
- The bacteria found in acute sinusitis are increasingly growing resistant to beta lactams and macrolides but remain sensitive to the late generation fluoroquinolones such as levofloxacin gatifloxacin, and moxifloxacin (Sinus and Allergy Health Partnership, 2004).

Clinical Presentation

- Acute sinusitis is defined as the ‘symptom complex accompanying inflammation of the sinuses present for less than 8 weeks in adults and 12 weeks in children’ (Kaliner et al 1997).

- Clinical presentation of acute bacterial sinusitis often follows a viral upper respiratory tract infection (URI) and persistence of the infection for more than 7-10 days usually indicates the development of sinusitis (Kaliner et al 1997).

Diagnostic Factors Predictive of Sinusitis Adapted from Brook I, Gooch WM, Jenkins SG, et al. Medical management of acute bacterial sinusitis. Recommendations of a clinical advisory committee on pediatric and adult sinusitis. *Ann Otol Rhinol Laryngol* 2000;109:2-20.	
Major Factors	• Facial pain or pressure (requires another major factor for diagnosis) • Facial congestion or fullness • Nasal obstruction • Nasal purulence or discolored postnasal discharge • Hyposmia or anosmia • Fever (acute sinusitis only)
Minor Factors	• Headache • Halitosis • Fatigue • Dental pain • Cough • Ear pain, pressure, or fullness • Fever (non-acute sinusitis)
Based on data from Lanza and Kennedy	

Place of Product in Therapy

- Fluoroquinolones have been recommended for first-line treatment of acute sinusitis for those with moderately severe disease and beta-lactam allergies or antibiotic treatment in the prior 4 to 6 weeks (Martin et al 2002).
- A table below represents antibiotic treatment guidelines for acute bacterial rhinosinusitis (ABRS) developed by the Sinus and Allergy Health Partnership, 2000.

Recommended Antibiotic Therapy for Adults with Acute Bacterial Rhinosinusitis Adapted from Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngology Head and Neck Surgery* 2004; 130(suppl)):S1-S45.		
	Initial Therapy	**Switch Therapy Options (No Improvement or Worsening after 72 hours)[a]**
Mild disease[b] with no recent antimicrobial use (past 4-6 weeks)[c]	• Amoxicillin/clavulanate (1.75-4 g/day)[c,d]	
	• Amoxicillin (1.5- 4g/day)[d]	• **Levofloxacin/** gatifloxacin/ moxifloxacin
	• Cefpodoxime proxetil	• Amoxicillin/clavulanate 4g/ 250mg
	• Cefuroxime axetil	• Ceftriaxone
	• Cefdinir	• Combination therapy[e]

	• Beta Lactam Allergic[f:]
	  • TMP/SMX
	  • Doxycycline
	  • Azithromycin, clarithromycin, erythromycin
	  • Telithromycin
		• **Levofloxacin**/ gatifloxacin/ moxifloxacin
		• Rifampin plus clindamycin

Mild disease[b] with recent antimicrobial use (past 4-6 weeks) or moderate disease[b]	• **Levofloxacin/** Gatifloxacin/ Moxifloxacin	• Re-evaluate patient[g]
	• Amoxicillin/clavulanate (4g/ 250mg)	• Re-evaluate patient[g]
	• Ceftriaxone	• Re-evaluate patient[g]
	• Combination Therapy[e]	• Re-evaluate patient[g]

	• Beta Lactam Allergic[f]:
	  • **Levofloxacin**/ gatifloxacin/ moxifloxacin
	  • Clindamycin and rifampin[h]
		• Re-evaluate patient[g]

[a]When a change in antibiotic therapy is made, the clinician should consider the limitations in coverage of the initial antibiotic. The respiratory fluoroquinolones (levofloxacin, gatifloxacin , and moxifloxacin), ceftriaxone, and amoxicillin/ clavulanate (4g/ 250mg) currently have the best coverage for both *S. pneumoniae* and *H. influenzae*. The terms mild and moderate are designed to aid in selecting antibiotic therapy. [b]The difference in severity of disease does not imply the presence or absence of antimicrobial resistance. Rather, this terminology indicates the relative degree of acceptance of possible therapeutic failure, and the likelihood of achieving spontaneous resolution of symptoms. The determination of disease severity lies with the clinician's evaluation of the patient's history and clinical presentation. Severe, life-threatening infection, with or without complications, is not addressed in these guidelines. [c]Prior antibiotic therapy within 4 to 6 weeks is a risk factor for infection with resistant organisms. Antibiotic choices should be based on this and other risk factors. [d]The total daily dose of amoxicillin and the amoxicillin component of amoxicillin/ clavulanate can vary from 1.5 to 4g/day. Lower daily doses (1.5g/day) are more appropriate in mild disease in patients with no risk factors for infections with a resistant pathogen (including recent antibiotic use). Higher daily doses (4g/day) may be advantageous in areas with a high prevalence of penicillin-resistant *s. pneumoniae* or DRSP, for patients with moderate disease, for patients who may need better *H. influenzae* coverage or for patients with risk factors for infection with a resistant pathogen. There is a greater potential for treatment failure or resistant pathogens in these patient groups. [e]Based on in vitro spectrum of activity: combination therapy using appropriate gram-positive and –negative coverage may be appropriate. Examples of combination therapy regimens include high-dose amoxicillin (4g/day) or clindamycin plus cefixime, or high-dose amoxicillin (4g/day) or clindamycin, plus rifampin. There is no clinical evidence at this time, however, of the safety or efficacy of these combinations. [f]Cephalosporins should be considered initially for patines with penicillin intolerance/ non-Type I hypersensitivity reactions (e.g. rash). TMP/SMX, doxycycline, macrolides, azalides, and ketolides are not recommended unless that patient is beta-lactam allergic. Their effectiveness against the major pathogens of ABRS is limited, and bacterial failure of 20% or 25% is possible. A respiratory fluoroquinolone (e.g. levofloxacin, gatifloxacin, moxifloxacin) is recommended for patients who have allergies to beta-lactams or who have recently failed other regimes. [g]Reevaluation is necessary because the antibiotics recommended for initial therapy provide excellent activity against the predominant ABRS pathogens, including *S. pneumoniae* and *H. influenzae*. Additional history, physical examination, cultures, and/or CT scan may be indicated, and the possibility of other less common pathogens considered. [h]Rifampin is a well-known inducer of several cytochrome p450 isoenzymes and therefore has a high potential for drug interactions.

- Levofloxacin is indicated for the treatment of acute maxillary sinusitis caused by *S. pneumoniae, H. influenzae, or M. catarrhalis.*
- Levofloxacin 500 mg QD provided similar efficacy with fewer reported adverse events than amoxicillin-clavulanate TID or clarithromycin BID in three comparative trials evaluating the treatment of acute bacterial sinusitis.

- **Noncomparative Data:**

Sydnor et al published the results of a non-comparative study that evaluated the safety and efficacy of levofloxacin (500 mg orally once daily for 10 to 14 days) in treating adult outpatients with acute bacterial sinusitis. A total of 329 patients were enrolled at 24 centers. Clinical response was assessed on the basis of signs and symptoms and sinus radiograph or computed topography results. Microbiologic cure rates were determined

on the basis of presumed plus documented eradication of the pre-therapy pathogen(s). The most common pathogens were *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus,* and *Moraxella catarrhalis*. Of 300 clinically evaluable patients, 175 (58%) were cured and 90 (30%) were improved at the post-therapy evaluation, resulting in a clinical success rate of 88%. Thirty-five patients (12%) clinically failed treatment. The microbiologic eradication rate (presumed plus documented) among 138 microbiologically evaluable patients was 92%. All but one of the 265 patients who were cured or improved at post- therapy returned for a long-term follow-up visit; 243 (92%) remained well 4 to 6 weeks after therapy and 21 (8%) had a relapse of symptoms. Twenty-nine patients (9%) reported adverse events considered to be related to levofloxacin. The most common drug-related adverse events were diarrhea, flatulence, and nausea; most adverse events were mild to moderate in severity. According to the authors, the results of this study indicate that levofloxacin 500 mg once daily is a safe and effective treatment for acute bacterial sinusitis (Sydnor et al., *Ann Allergy Asthma Immunol* 1998).

Francisco performed a non-comparative, multicenter, prospective trial in 65 patients to determine the effectiveness of levofloxacin in patients with acute bacterial sinusitis. The dose of the levofloxacin was 500 mg PO each day and the mean duration was 8.1 days. Levofloxacin therapy was considered to have failed if the patients taking levofloxacin experienced persistent signs and symptoms of infection after 72 hours of treatment and/or they had worsening of the symptoms of infection. Fifty-eight patients were evaluated for clinical efficacy and a statistically significant improvement was achieved in terms of sinus pain, nasal obstruction, purulent rhinorrhea, and local sinus pain ($p<0.05$). Global success rate, which refers to both cure and improvement of symptoms, was 96% at the end of the treatment. Adverse events were only seen among 6% of patients and included nausea, palpitations, headache, and tremor. The author concluded that levofloxacin is safe and effective when given on a daily basis for the treatment of acute sinusitis in adult patients (Francisco et al., 9th *ICID* 2000).

- **Comparative Data:**

Levofloxacin vs. Clarithromycin

Lasko et al conducted a double-blind study in 236 adult patients with acute sinusitis who were randomized to receive oral levofloxacin 500 mg orally once daily (n=119) or oral clarithromycin 500 mg twice daily (n=117) for 10-14 days. Between 2 and 5 days after therapy, participants were evaluated as cured (no symptoms), improved (symptoms improved, no further therapy required), or failed (further therapy required). Clinical response rates (cured plus improved) for clinically evaluable patients were 93.9% for levofloxacin (n=98) and 93.5% for clarithromycin (n=93). The proportion of patients evaluated as cured was higher in the levofloxacin (40.8%) than in the clarithromycin arm (29.0%) and individual symptoms showed higher rates of resolution. Of patients receiving levofloxacin and clarithromycin, 22.5% and 39.3%, respectively, experienced adverse events related or possibly related to the study therapy. The results of this study showed that once daily levofloxacin therapy is as effective as twice-daily clarithromycin

therapy in acute sinusitis, with more complete clearing of symptoms and better tolerability (Lasko et al., *J Int Med Res* 1998).

Adelglass et al conducted a multicenter, investigator-blinded, randomized, parallel-group study comparing oral levofloxacin 500 mg once daily for 14 days with oral clarithromycin 500 mg twice daily for 14 days in the treatment of acute bacterial sinusitis. Of 216 adult outpatients randomized to treatment, 190 were evaluable for efficacy. The primary efficacy measure was clinical response, based on resolution of signs and symptoms 2 - 5 days after therapy. A secondary efficacy measure was relapse rate 1 month after therapy. Among evaluable patients, clinical success rates (cured or improved) were 96.0% and 93.3% for levofloxacin and clarithromycin, respectively (95% CI - 9.2%, 3.7%). In all, 4.1% of patients receiving levofloxacin and 7.2% receiving clarithromycin had a relapse of symptoms 1-month after therapy (95% CI -12.2%, 3.2%). Long-term success (initial success, absence of relapse at 1 month, no further antibacterial therapy 2-5 days after therapy) was 79.2% in the levofloxacin group and 76.4% in the clarithromycin group (95% CI -14.7%, 9.0%). Based on investigator- assessed treatment-emergent adverse events, overall tolerability of the drugs was similar, except for a higher frequency of taste perversion and diarrhea in the clarithromycin group. Levofloxacin had a statistically significant advantage over clarithromycin based on two quality-of-life (QOL) parameters: number of times taking other drugs for targeted medical conditions and mean total cost of these drugs. No statistical significance was found in other QOL variables. These findings suggest that the efficacy and tolerability of levofloxacin 500 mg once daily are comparable with those of clarithromycin 500 mg twice daily in the treatment of acute bacterial sinusitis (Adelglass et al., *Pharmacotherapy* 1998).

Levofloxacin vs. Amoxicillin/Clavulanate

Adelglass et al reported the results of a comparative trial in outpatients with acute sinusitis, randomly assigned to receive levofloxacin (500 mg orally once daily) or amoxicillin-clavulanate (500/125 mg orally 3 times daily) for 10 to 14 days. The success rates (cured and improved) 2 to 5 days after the end of treatment were 88.4% for the 267 clinically evaluable patients who received levofloxacin and 87.3% for the 268 clinically evaluable patients who received amoxicillin-clavulanate. Drug-related adverse events occurred in a smaller percentage of patients in the levofloxacin treatment group (7.4%) than in the amoxicillin-clavulanate treatment group (21.2%). The most common of these were nausea, diarrhea, vaginitis, and abdominal pain for levofloxacin-treated patients and diarrhea, vaginitis, nausea, genital moniliasis, abdominal pain, vomiting, and flatulence for amoxicillin-clavulanate-treated patients. The results of this study demonstrate that once-daily administration of levofloxacin is as effective and better tolerated than amoxicillin-clavulanate administered 3 times daily for treating acute sinusitis in adult outpatients (Adelglass et al., *Otolaryngol Head Neck Surg* 1999).

B. SKIN AND SKIN STRUCTURE INFECTIONS

a. ***Complicated Skin and Skin Structure Infections*** (File et al., *Am J Surg* 1995; Gentry *J Antimicrob Chemother* 1991; Nichols, *J Antimicrob Chemother* 1999)

Burden of Disease

- Skin infections are considered complicated when they are associated with underlying conditions such as poor circulation or vascularization, diabetes, surgery, or trauma.
- Diabetic foot ulcers, postoperative infections, bites, and abscesses all may be considered complicated skin infections.
- Approximately > 200,000 surgical wound infections are estimated annually in the United States.

Etiology

- Complicated skin infections are often polymicrobial and may be caused by a mixture of aerobic and anaerobic pathogens.
- Organisms may include: *S. aureus*, β-hemolytic streptococci, enterococci, Enterobacteriaceae, *Pseudomonas* sp., *Clostridium* sp., and *Bacteroides* sp.

Clinical Presentation

- SSSIs can be considered complicated when surgical intervention is required and/or infectious process, which is suspected or confirmed to involve deeper soft tissue (fascia and/or muscle layers).

Place of Product in Therapy

- Antimicrobial therapy of many skin infections must be directed toward a wide variety of pathogens.
- In addition to exhibiting broad-spectrum activity, appropriated therapy should provide excellent tissue penetration.

Empiric Therapy of Skin Infections, including Necrotizing & Secondary Skin Infections (File, 1995)	
Antimicrobial Agents	**Microorganisms**
• **Second generation cephalosporins** • **Imipenem/cilastatin** • **β-lactamase inhibitor combinations**: Piperacillin/tazobactam Ticarcillin/clavulanate Ampicillin/sulbactam	• To cover *S. aureus*, β-hemolytic streptococci, enterococci, Enterobacteriaceae, *Pseudomonas* sp., *Clostridium* sp., and *Bacteroides* sp.
• **Antimicrobial Combinations:** Clindamycin or metronidazole + Broad spectrum β-lactam (piperacillin, a 3rd	• To cover *Staphylococcus*, anaerobes, and gram-negative organisms

generation cephalosporin, or aztreonam), a **fluoroquinolone**, or an aminoglycoside	
Vancomycin parenteral therapy	• For methicillin-resistant *S. aureus*

- Levofloxacin is indicated for complicated SSSIs due to methicillin-sensitive *S. aureus*, *E. faecalis*, *S. pyogenes*, or *P. Mirabilis*.
- Pharmacokinetic studies have demonstrated that levofloxacin penetrates effectively into skin and skin structures at 750 mg doses and reaches peak tissue concentrations that should be effective against most of the common pathogens causing complicated SSSIs.

- **Comparative Data:**

Levofloxacin vs. Ticarcillin/Clavulanate ± Amoxicillin/Clavulanate

A multicenter, open-label, randomized (1:1) study that enrolled 399 patients was conducted to compare the efficacy and safety of levofloxacin 750-mg once-daily intravenously (IV), orally (PO), or IV/PO versus ticarcillin/clavulanate 3.1-g Q4-6H IV alone or followed by oral amoxicillin/clavulanate 875-mg Q12H for the treatment of complicated skin and skin-structure infections (SSSIs). The mean duration of treatment period was 10.1 ± 4.7 days for the levofloxacin group and 12.1 ± 4.9 for the ticarcillin/clavulanate ± amoxicillin/clavulanate group. The clinical success rate was assessed based on the signs and symptoms of SSSIs recorded at the on post-therapy visit (2-5 days after completion of therapy). The microbiological efficacy was determined based on the results of the sample cultures obtained at the post-therapy visit from the original infection site. The overall clinical success rates (improved and cured) were 84.1% (116/138 clinically evaluable patients) in the levofloxacin treatment group compared to 80.3% (106/132 clinically evaluable patients) in the ticarcillin/clavulanate ± amoxicillin/clavulanate treatment group. Clinical response rates of various type of diagnosis in each treatment group are presented as follows:

Diagnosis	Levofloxacin	Ticarcillin/clavulanate ± amoxicillin/clavulanate
Major abscess	90%	90%
Wound infection	88.7%	85.4%
Infected with non-diabetic ulcer	62.5%	72.7%
Infected with diabetic ulcer	69.2%	57.1%
Other	90.9%	100%

Surgical procedures (incision and drainage or debridement) were also performed in both levofloxacin and ticarcillin/clavulanate ± amoxicillin/clavulanate treatment groups (45% and 44%, respectively), either shortly before or during the antibiotic treatment. (Graham et al., 11th *ICID* 2002) Of the 98 microbiologically evaluable patients in each study group, the eradication rates were 83.7% and 71.4% (95% CI, -24.3 to -0.2) for the levofloxacin and the ticarcillin/clavulanate ± amoxicillin/clavulanate, respectively. The results of eradication rates that were based on pathogen category (gram-positive & gram-negative aerobes, gram-positive & gram-negative anaerobes) were comparable in both study

groups. Overall, levofloxacin and ticarcillin/clavulanate ± amoxicillin/clavulanate were well tolerated. The authors concluded that levofloxacin 750-mg given PO and/or IV once daily was as effective and safe as ticarcillin/clavulanate ± amoxicillin/clavulanate for the treatment of complicated SSSIs (Graham et al., *Clin Infect Dis* 2002).

b. ***Uncomplicated Skin and Skin Structure Infections*** (File et al., *Am J Surg* 1995)

Burden of Disease

- Bacterial infections of the skin and skin structure comprise a diverse collection of diagnoses, ranging from mild superficial lesions to life-threatening infections.

Etiology

- These infections are often caused by a single organism, most commonly *S. aureus* and to a lesser extent, *S. pyogenes*.

Clinical Presentation

- Clinical signs and symptoms may include pain, swelling, erythema, edema, indurated lesion sharply circumscribed by an elevated border, fluid-filled vesicles, pus-filled blisters, accompanied by fever, malaise, and tender lymphadenopathy.
- These characterizations may vary or be specific to the type of primary skin infections.

Place of Product in Therapy

- The established spectrum of levofloxacin includes coverage for both S. aureus (MSSA) and S. pyogenes, the primary pathogens for uncomplicated skin infections.
- Levofloxacin has been demonstrated to be a safe, effective, and well-tolerated drug with convenient once daily dosing.
- Levofloxacin is indicated for the treatment of mild to moderate uncomplicated skin and skin structure infections due to *Staphylococcus aureus* and *Streptococcus pyogenes*.

- **Comparative Data:**

Levofloxacin vs. Ciprofloxacin

Nichols et al reported a multicenter, open-label, active-controlled, randomized study to compare the efficacy and safety of oral levofloxacin 500-mg QD for 7 to 10 days (N=231) with oral ciprofloxacin twice daily for 7-10 days (N=238) in adults with mild to moderate skin and skin structure infections. Levofloxacin was shown to be effective, well tolerated, and safe, with a clinical and microbiologic efficacy profile comparable to that of ciprofloxacin. Among evaluable patients, 97.8% (178/182) of levofloxacin-treated patients, and 94.3% (182/193) ciprofloxacin-treated patients were considered a clinical success (NS). The overall microbiologic eradication rates were 97.5% (153/157) and 88.8% (135/152) for levofloxacin and ciprofloxacin, respectively. Levofloxacin eradicated 100% of the two most common pathogens in skin and skin structure infections, *S. aureus* (87/87), and *S. pyogenes* (14/14), compared to ciprofloxacin 87.4% (76/87) and 90.0% (18/20), respectively. Similar rates of adverse events were seen in both groups. These findings support the efficacy of levofloxacin once daily 500 mg for 7

to 10 days for the treatment of mild-to-moderate skin and skin structure infections due to common etiologic agents (Nichols et al., *Southern Medical Journal* 1997).

Nicodemo et al compared levofloxacin 500-mg QD for 7 days with ciprofloxacin-500 mg twice daily for 10 days in 272 patients with uncomplicated skin and skin structure infections. Two hundred fifty-three subjects were evaluable for efficacy (129 levofloxacin, 124 ciprofloxacin). Clinical response was the primary efficacy variable studied. Patients were evaluated pre-therapy, 3 to 5 days after starting treatment and 1 to 10 days post-treatment. Clinical success rates were 96.1% and 93.5%, respectively. *S. aureus* and *S. pyogenes* were the most commonly isolated bacteria, eradication rates for ciprofloxacin were 93% and 92%, levofloxacin eradicated 94% of both pathogens. Overall microbiological eradication rates were 93% and 90%, respectively (Nicodemo *IJCP* 1998).

Levofloxacin vs. Gatifloxacin

In a double blind, multicenter trial the safety and efficacy of gatifloxacin was compared to levofloxacin in patients with uncomplicated skin and soft tissue infections (SSTIs). Patients were randomized to receive levofloxacin 500 mg (n=207) or gatifloxacin 400 mg (n=202) orally, once a day for 7 to 10 days. Seven to 14 days after therapy completion, clinical cure rates were reported for the clinically evaluable patients as 91% for those who received gatifloxacin and 84% for levofloxacin. Among the microbiologically evaluable patients, cure rates were 93% and 88% for gatifloxacin and levofloxacin, while both drugs eradicated 92% of all isolated pathogens. The drug related adverse events most commonly reported include nausea (8% for each drug), diarrhea (6% for each drug), vaginitis (8 and 4% for gatifloxacin and levofloxacin), and headache (3 and 5%, respectively). The authors concluded that levofloxacin and gatifloxacin were comparable in the treatment of uncomplicated SSTIs (Tarshis et al., *Antimicrob Agents Chemother* 2001).

C. GENITOURINARY INFECTIONS

a. *Complicated Urinary Tract Infections & Acute Pyelonephritis* (Warren et al., *Clin Infect Dis* 1999; Stamm et al., *N Eng J Med* 1995)

Burden of Disease

- Complicated UTIs are defined as those occurring in catheterized patients or in patients with functional or anatomical abnormalities.
- Predisposing conditions include the presence of a stone, stricture, neurogenic bladder, or narrowing of the urethra (caused by prostate enlargement or neoplasia). Complicated UTIs may also be caused by a resistant pathogen.

Etiology

- Although complicated UTIs may be polymicrobial, *E. coli* is the most commonly isolated pathogen.
- Organisms include *E. coli*, *Proteus* sp., *Klebsiella* sp., *Pseudomonas* sp., Enterococci, and *Staphylococci.*

Clinical Presentation

- Dysuria
- Frequency
- Urgency
- Suprapubic or lower back (not flank) pain

Place of Product in Therapy

- Therapeutic approaches to treatment require antimicrobials with broad spectra of activity because complicated UTIs have a less predictable microbiological etiology than uncomplicated UTIs.
- Levofloxacin is indicated for the treatment of mild to moderate complicated urinary tract infections caused by *Enterococcus faecalis*, *Enterobacter cloacae*, *E. coli*, *K. Pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*.
- Levofloxacin is indicated for the treatment mild to moderate of acute pyelonephritis caused by *E. coli*.

IDSA Guidelines **Empirical Therapy for Acute Pyelonephritis** Adapted from Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis* 1999;29:745-758.	
Outpatients	• **Oral fluoroquinolone** • Oral trimethoprim-sulfamethoxazole as an alternative if the organism is susceptible • For gram positive organism: Amoxicillin or amoxicillin/clavulanic acid
Patients requiring hospitalization	• Parenteral **fluoroquinolone**, an aminoglycoside with or without

	ampicillin or an extended spectrum cephalosporin with or without an aminoglycoside • For gram positive coca: Ampicillin/sulbactam with or without an aminoglycoside • After clinical improvement, change to an oral regimen recommended above

- The efficacy and safety of oral levofloxacin 250 mg (10 days) for the treatment of complicated UTIs including pyelonephritis has been demonstrated in three published studies.
- In two comparative studies, levofloxacin demonstrated therapeutic equivalence to ciprofloxacin and lomefloxacin with few adverse events, which were mild to moderate in severity.

- **Comparative Data:**

Levofloxacin vs. Ciprofloxacin vs. Lomefloxacin

Two randomized, multi center trials were conducted to evaluate the safety and efficacy of levofloxacin versus that of ciprofloxacin and lomefloxacin in adult patients with complicated urinary tract infections (UTI) or acute pyelonephritis. Study 1 was a double-blind trial in which patients received levofloxacin 250 mg (once daily) or ciprofloxacin 500 mg (twice daily) for ten days. In the second study, which was open-label, patients received either 7- 10 days of levofloxacin 250 mg (once daily) or 14 days of lomefloxacin 400 mg (once daily). Microbiologic eradication rates ranged from 94-95% after 5-9 days of therapy and 94% post-therapy for all three antimicrobial agents. Clinical cure response rates for the studies when combined was 92% for levofloxacin (n=89), 88% for ciprofloxacin (n=58), and 80% for lomefloxacin (n=39). Drug related adverse events were experienced in 2% of levofloxacin, 8% of ciprofloxacin, and 5% of lomefloxacin patients (Richard et al., *Urology* 1998).

Levofloxacin vs. Ciprofloxacin

Richard et al evaluated the safety and efficacy of levofloxacin (250 mg once daily) with ciprofloxacin (500 mg twice daily) in adults with complicated UTIs. Patients were treated for 10 days in this randomized, double blind, multi center study. Of the 239 patients who were clinically evaluable, clinical success rates were 92.1% for levofloxacin and 88.5% for ciprofloxacin while microbiologic response was 91% versus 93% respectively at post-therapy. Drug related adverse events were reported in 3.6% of levofloxacin treated patients and in 2.7% of the patients who received ciprofloxacin (Richard et al., *Pharmacy and Therapeutics* 1998).

Levofloxacin vs. Lomefloxacin

Adult patients with complicated UTIs were included in this randomized, open-label, multi center trial to assess the safety and efficacy of levofloxacin 250 mg (7-10 days) with lomefloxacin 400 mg (14 days) given once daily. In 336 patients, no statistical difference

was observed between levofloxacin and lomefloxacin in microbiological eradication rates (95.3% vs. 92.1% respectively) or clinical cure rates (84.8% vs. 82.4% respectively). Adverse events considered to be drug related were reported to be mild to moderate in severity for both levofloxacin (4.3%) and lomefloxacin (7.9%) (Kimberg et al., *Urology* 1998).

b. Uncomplicated Urinary Tract Infections (Warren et al., *Clin Infect Dis* 1999; Stamm et al., *N Eng J Med* 1995)

Burden of Disease

- Uncomplicated UTIs occur mostly in young, sexually active females.
- UTIs account for more than 7 million visits to physicians' offices each year.
- Although they are generally mild, the frequency of recurrent infections is associated with significant morbidity in an otherwise healthy population.

Etiology

- The common pathogens for uncomplicated UTIs include *E. coli, S. saprophyticus, and K. Pneumoniae.*

Clinical Presentation

- Dysuria
- Frequency
- Urgency
- Suprapubic or lower back (not flank) pain

Place of Product in Therapy

- An antimicrobial of choice must reach high levels and retain bactericidal activity at the typically low pH of urine.
- Short-course (three-day) levofloxacin 250 mg has been shown to be a safe and effective treatment option for uncomplicated UTIs.
- Levofloxacin is indicated for the treatment of uncomplicated UTIs due to *E. coli, K. pneumoniae*, or *Staphylococcus saprophyticus*.

- **Comparative Data:**

Levofloxacin vs. Ofloxacin

Richard et al conducted a double-blind, multicenter trial where 545 subjects having uncomplicated urinary tract infections were randomized to receive either levofloxacin 250 mg once daily or ofloxacin 200 mg twice daily for 3 days. Symptoms were improved or cured in 98.1% of the levofloxacin subjects and 97% of the ofloxacin subjects. Of the 545 subjects, 157 levofloxacin and 165 ofloxacin patients were microbiologically evaluable. Eradication rates at 5 to 9 days post-therapy were 96.3% in the levofloxacin group and 93.6% in the ofloxacin group. Levofloxacin was shown to be effective for the treatment of uncomplicated urinary tract infections. Drug-related adverse effects occurred in 3.4% of the 298-levofloxacin subjects and 7.5% of the 293-ofloxacin subjects. Four of the ofloxacin subjects discontinued therapy due to adverse reactions, while none of the levofloxacin subjects discontinued therapy due to adverse reactions (Richard et al., *Infect Dis Clin Pract* 1998).

Gupta et al conducted an uncontrolled, prospective study to determine both the safety and feasibility of patient-initiated treatment of recurrent uncomplicated urinary tract infections. One hundred seventy two women were instructed to initiate therapy with either 200 mg ofloxacin twice daily or 250 mg levofloxacin once daily for 3 days if they developed symptoms suggestive of a urinary tract infection. Of the 172 women, 88 self-diagnosed a total of 172 urinary tract infections. Ninety-four percent of these 172 suspected cases met the criteria for probable or definite urinary tract infection. Of the culture-confirmed episodes (144 cases), the total clinical cure rate was 92% and the total microbiological cure rate was 96% with no serious adverse events reported (Gupta et al., *Ann Int Med* 2001).

c. Chronic Bacterial Prostatitis (Bjerklund et al. *Eur Urol* 1998; Lloyd et al. *Curr Infect Dis Rep* 2001; Association of Genitourinary Medicine *Sex Transm Infect* 1999; Lummus et al. *Emergency Medicine Clinics of America* 2001; Fowler. *Urol* 2002)

Burden of Disease

- Prostatitis has an estimated prevalence of 10% among the male population at large and represents over 2 million medical office visits per year in the United States.
- About half of the adult male population will experience symptoms of prostatitis at some point and it results in about 25% of all urologist office visits.
- It is the most common urologic diagnosis in men below the age of 50 and the third most common in men greater than 50.
- Bacterial prostatitis (acute and chronic) account for 5-10% of cases of prostatitis.
- Annual direct costs associated with outpatient treatment of prostatitis are estimated to be roughly $1,000 - $1,200 per patient. The cost for antibiotics and other necessary medications alone average $300, or roughly 30% of the total costs. (Overmyer M. *Urology Times* 2001; Stevermer et al. *Am Fam Physician* 2000)
- The indirect costs associated with prostatitis primarily include the effects of recurrent urinary symptoms, pain, and sexual dysfunction on the patient's productivity and quality of life. (Overmyer M. *Urology Times* 2001, Lobel et al. *World J Urol* 2003; Nickel, 2003)

Etiology

- The most common pathogen is believed to be *Escherichia coli,* which historically accounted for up to 80% of cases of chronic bacterial prostatitis.
- Gram positives, including *Staphylococcus aureus*, *Enterococcus faecalis*, and coagulase-negative staphylococci, are increasingly playing a role in chronic bacterial prostatitis.
- A recent study of patients with chronic bacterial prostatitis found that the most common admission pathogens were gram positive. They included *Enterococcus faecalis* (n=99), *Staphylococcus epidermidis* (n=53), *Staphylococcus haemolyticus* (n=41); *Escherichia coli* (n=26), *Streptococcus agalactiae* (n=39), *Streptococci mitis* (n=20) and coagulase negative *Staphylococci* (n=19) (Kahn, et al., 42nd ICAAC 2002).
- These results were similar to another recent study, which compared the efficacy of gatifloxacin and ciprofloxacin in the treatment of chronic bacterial prostatitis. The most prevalent pathogens were *E. faecalis* (40%), *S. epidermidis* (21%), and *E. coli* (11%) (Hindes 40th IDSA 2002).

Clinical Presentation

- Subacute illness characterized by mild urinary irritative symptoms (frequency, urgency, and dysuria) and possible complaints of back pain, scrotal or perineal pain, hematospermia, painful ejaculation, or voiding dysfunction such as urgency, frequency, hesitancy, or slow stream. Symptoms must be present for more than 3 months.

- Classification of chronic prostatitis depends on degree of prostatic inflammation and the microbiologic results of the expressed prostatic secretions obtain via the Meares-Stamey method. Inflammatory cells in the prostatitic fluid and positive cultures for an offending pathogen are diagnostic for chronic bacterial prostatitis.

Place of Product in Therapy

- In order for an antibiotic to be effective in chronic bacterial prostatitis, it must achieve sufficient penetration of the prostate and prostatic fluid. To penetrate the prostate epithelium, the agent must be lipid soluble and have a pKa that allows it to remain unionized in the prostatitic fluid.
- Levofloxacin penetrates well into the prostate and achieves a prostate/plasma ratio of 2.96 (Drusano et al. *Antimicrobial Agents Chemother* 2000)
- Levofloxacin is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or *Staphylococcus epidermidis*.
- Fluoroquinolones are recommended first-line for the treatment of chronic bacterial prostatitis. Trimethoprim-sulfamethoxazole and tetracycline are alternative choices. The recommendations for duration of treatment range from 4 weeks to 3 months.
- The national guideline for the management of prostatitis developed by the Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases is presented in the table below:

National Guideline for the Management of Prostatitis Treatment of Chronic Bacterial Prostatitis Adapted from Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases. Sex Transm Inf 1999;75 (Suppl1):S46-S50	
Recommended Regimen	**Alternative (For those allergic to quinolones)**
Quinolone such as: • Ciprofloxacin 500 mg twice daily for 28 days • Ofloxacin 200 mg twice daily for 28 days • Norfloxacin 400 mg twice daily for 28 days	• Minocycline or doxycycline 100 mg twice daily for 28 days • Trimethoprim 200 mg twice daily for 28 days • Trimethoprim-Sulfamethoxazole 960 mg twice daily for 28 days

- **Comparative Data:**

Levofloxacin vs. Ciprofloxacin

A multicenter, double-blind trial was conducted to compare the efficacy and safety of oral levofloxacin 500 mg QD to oral ciprofloxacin 500 mg BID for 28 days in the treatment of chronic bacterial prostatitis (CBP). Adult men with a history of CBP, current clinical signs and symptoms of prostatitis, and laboratory evidence of prostatitis were enrolled. Microbiological culture results from urine samples collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) obtained via the Meares-Stamey procedure were necessary for study inclusion. The primary efficacy endpoint was microbiologic

efficacy in the microbiologically evaluable patient population (N=136 for the levofloxacin group; N=125 for the ciprofloxacin group). The overall microbiological response rates 5-18 days after completion of therapy were 75% and 76.8% for levofloxacin and ciprofloxacin, respectively (95% CI:-12.58, 8.95). The table below contains overall eradication rates for indicated pathogens:

Pathogen	**Levofloxacin % (n/N)**	**Ciprofloxacin % (n/N)**
E. coli	93.3% (14/15)	81.8% (9/11)
E. faecalis	72.2% (39/54)	75.0% (33/44)
*S. epidermidis**	81.8% (9/11)	78.6% (11/14)

* Eradication rates are shown only for patients who had a sole pathogen only; mixed cultures were excluded.

This finding differs from previous thought that gram-negative rods were most commonly isolated in CBP. The overall clinical success rates (cure plus improvement with no need for further antibiotic therapy) in the microbiologically evaluable population 5-18 days after completion of therapy were 75% and 72.8% for levofloxacin and ciprofloxacin, respectively (95% CI: -8.87, 13.27). Clinical long-term success rates at six-months post-therapy were comparable for levofloxacin and ciprofloxacin (70.5% versus 71.1%, respectively). Overall, levofloxacin was found to be equivalent to ciprofloxacin in the treatment of CBP (Kahn et al. 42nd ICAAC 2002).

4. NATIONAL SURVEILLANCE DATA

A. Tracking Resistance in the US Today (TRUST)

- TRUST 8 is the 8th consecutive multi-center surveillance for respiratory pathogens that evaluated the current prevalence of antimicrobial resistance among *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. Additionally, TRUST 8 evaluated antimicrobial resistance among gram-negative organisms such as *E. cloacae* and *P. aeruginosa*.

- From October 2003 through May 2004, isolates were examined for their susceptibility to levofloxacin and other commonly prescribed antimicrobials.

- From over 200 U.S hospital laboratories spanning all 50 states in the U.S., the District of Columbia, and Puerto Rico, 4,309 isolates of *S. pneumoniae* were collected.

- Isolates were submitted to Focus Technologies' central laboratory in Herndon, VA, for antimicrobial susceptibility testing by broth microdilution (NCCLS reference method).

- Of the 4,309 *S. pneumoniae* isolates tested, 771 (18.0%) were penicillin-resistant, 25.0% were resistant to azithromycin, 21.2% were resistant to trimethoprim-sulfamethoxazole, and 1.19% of the isolates were resistant to levofloxacin.

- Multi-drug resistant (defined as resistance to ≥ 2 antimicrobial classes) isolates accounted for 26.3% of all S. pneumoniae isolates. Of the multi-drug resistant strains, 98% were susceptible to levofloxacin.

- Susceptibility rates of various gram-negative bacilli to levofloxacin were greater than 90% for organisms such as *H. influenzae, K. pneumoniae, E. cloacae,* and *S. marcescens.*

- Over 99% (n=1207) of *H. influenzae* isolates were susceptible to levofloxacin, and the levofloxacin MIC_{90} for *M. catarrhalis* remained stable at 0.06 μg/mL.

- Levofloxacin MIC (MIC_{90} of 1.0 μg/mL for *S. pneumoniae*) distribution has remained stable over the past 8 years of surveillance (1997-2004).

B. *Streptococcus pneumoniae* Susceptibility

- **Summary of % Resistance against *Streptococcus pneumoniae* during 8 consecutive respiratory seasons in the United States: TRUST 1-8**

Antimicrobial	%R 1996-1997 TRUST 1	%R 1997-1998 TRUST 2	%R 1998-1999 TRUST 3	%R 1999-2000 TRUST 4	%R 2000-2001 TRUST 5	%R 2001-2002 TRUST 6	%R 2002-2003 TRUST 7	%R 2002-2003 TRUST 8
Levofloxacin	0.6	0.2	0.6	0.5	0.8	0.9	0.9	1.1
Penicillin	13.6	12.8	14.7	16	16.9	18.4	17.3	18.6
Amoxicillin-Clavulanate	11.2	9.9	10.5	14.2	2.7	4.2	4.1	5.2
Cefuroxime	22.6	22.9	25.2	27.4	22.8	22.7	20.7	20.2
Ceftriaxone	4.8	3.3	3.4	3.8	3.0	1.7	1.5	1.4
TMP-SMX	N/A	14.3	27.3	29.3	28.1	26	23.9	21.2
Azithromycin	N/A	21.1	22.7	23.4	27.5	27.5	27.5	25.0
Total number of *Streptococcus pneumoniae* isolates tested: 9,190 (TRUST 1); 4148 (TRUST 2); 4296 (TRUST 3); 9499 (TRUST 4); 6362 (TRUST 5); 7671 (TRUST 6); 4456 (TRUST 7); 4309 (TRUST 8)								

(Sahm et al. IDSA*, 2003; Data on File; Thornsberry et al.* Diagn Microbiol Infect Dis *1997; Thornsberry et al.* J Antimicrobial Chem *1999; Thornsberry et al.* Clin Infect Dis *2002; Thornsberry et al.* ICAAC *1998; Karlowsky et al.* Clin Infect Dis *2003)*

- **Cross Resistance Across the Fluoroquinolone Class**

Davies et al (*J Antimicrob Chem* 2003) examined the similarity among 68 (0.5%) of 1379 US clinical isolates of *Streptococcus pneumoniae* from the TRUST 3 (1998-1999) and TRUST 4 (1999-2000) surveillance studies that were resistant to levofloxacin (MIC > 8 mg/mL). Broth microdilution reference method was utilized to analyze susceptibility of the levofloxacin-resistant strains to ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin. All levofloxacin-resistant strains were analyzed using DNA sequencing of quinolone resistance determining region (QRDR) of topoisomerase IV and DNA gyrase genes, serotyping, and pulsed-field gel electrophoresis (PFGE). Fluoroquinolone-resistant isolates were identified from 48 of 288 institutions in 29 states during the TRUST 3 and 4 studies. The majority of the isolates (n= 46, 68%) were from inpatients. One isolate was from an unknown source. Ninety-one percent of the isolates were non-susceptible to all fluoroquinolones tested. All levofloxacin-resistant isolates were resistant to ciprofloxacin (MIC ≥ 4 mg/mL) and non-susceptible to gatifloxacin (6 isolates intermediate, 62 isolates resistant). Ninety-one percent of the isolates were also non-susceptible to moxifloxacin (36 isolates intermediate, 26 isolates resistant).

All levofloxacin-resistant isolates had two or more mutations within the QRDR of *parC, parE, gyrA,* and *gyrB*. The authors noted that isolates resistant to levofloxacin are usually cross-resistant to other fluoroquinolones and associated with at least two QRDR mutations.

Levofloxacin-resistant *S. pneumoniae* and cross-resistance to other fluoroquinolones for the 4,456 isolates from the TRUST 7 study (2002-2003) has been examined. Tested isolates were 99.0% susceptible to levofloxacin, with 43 isolates (0.96%) being resistant to levofloxacin. Of the levofloxacin-resistant isolates, none were susceptible to ciprofloxacin. Two isolates (4.4%) were susceptible to gatifloxacin and 6 isolates (13.3%) were susceptible to moxifloxacin.

Levofloxacin resistant *Streptococcus pneumoniae* necessitate $\geq$ 2 mutations in the resistance determining segment (QRDR) of topoisomerase IV and DNA gyrase. Davies et al (*ICAAC* 2001) evaluated the occurrence of single mutations in either topoisomerase IV or DNA gyrase in S*. pneumoniae* isolated, exposed to levofloxacin, from the 99-00 respiratory season (TRUST 4). Five hundred twenty eight (528) strains were randomly chosen and the QRDR section was tested for mutations. Changes in the QRDR region were reported as follows: 0 out of 270 isolates (MIC 0.5 µg/ml), 18 out of 244 strains (MIC 1 µg/ml), and 10 out of 14 isolates (MIC 2 µg/ml) expressed changes in topoisomerase IV. No mutations were detected in DNA gyrase. Of the 9438-levofloxacin susceptible strains from the 99-00 respiratory season, the evaluators estimated that 3.7% contained a single mutation in topoisomerase IV.

- **Resistance Patterns**

Karlowsky et al (*Clin Infect Dis* 2003) analyzed 27,828 isolates of *Streptococcus pneumoniae* from the TRUST data during 4 consecutive respiratory seasons (1998-2002) to identify factors associated with antimicrobial resistance. The prevalence of azithromycin and penicillin resistance increased by 4.8% to 27.5% and 3.7% to 18.4%, respectively. Ceftriaxone resistance increased by 0.5% to 1.7% compared to levofloxacin resistance increase of 0.3% to 0.9%. When analyzed according to patient age group, significantly ($p<0.00001$) higher rates of penicillin, azithromycin, and trimethoprim-sulfamethoxazole resistance were noted in patients < 18 years of age compared to patients 18-64 years of age. The prevalence of ceftriaxone resistance among patients < 18 years of age was modestly elevated (2.9%, 153 of 5,227 isolates) than in patients 18-64 years of age (1.3%, 163 of 12,761 isolates). Levofloxacin resistance was noted in only 3 of 5227 isolates (0.06%) among those <18 years of age, compared to 1% in patients > 64 years of age and 0.7% in patients 18-64 years of age. When analyzed by specimen source, the prevalence of penicillin, azithromycin, TMP-SMX, and levofloxacin resistance was significantly higher among lower respiratory tract isolates than among isolates recovered from blood samples ($p\leq 0.0001$). Penicillin resistance correlated with coresistance to levofloxacin, TMP-SMX, azithromycin, and ceftriaxone were: 1.3%, 87.3%, 76.3%, and 9.1%, respectively. Sixty-two of 27,828 isolates (0.2%) were concurrently resistant to penicillin and levofloxacin. Additionally, the differences in the prevalences of resistance across the 4 respiratory seasons in each of the 9 US Bureau of the Census regions were greatest for azithromycin (range, 4.8% to 14.9%), penicillin (range, 1.1% to 15.2%), and TMP-SMX (range, 2.2% to 12.1%). The percent resistance ranges were lower for levofloxacin (range, 0.5% to 1.9%) and ceftriaxone (range, 0.3% to 3.8%). The authors concluded that patient age, specimen source, and penicillin resistance were factors associated with antimicrobial resistance, particularly for non-fluoroquinolone antimicrobial agents.

C. Susceptibility of Gram Negative Organisms

- **Levofloxacin Susceptibility Trends**

	Year	Number of Isolates	MIC_{90} (μg/ml)	% Susceptibility
E. Cloacae				
TRUST 4	2000	297	1	95.6
TRUST 5	2001	309	2	91.6
TRUST 6	2002	417	2	92.3
TRUST 7	2003	312	2	91.3
TRUST 8	2004	589		92.5
E. Coli				
TRUST 4	2000	655	0.06	95.2
TRUST 5	2001	772	0.06	94.7
TRUST 6	2002	1076	0.25	93.1
TRUST 7	2003	915	0.5	90.9
TRUST 8	2004	1715		89.7
K. pneumoniae				
TRUST 4	2000	550	0.5	95.5
TRUST 5	2001	481	0.5	96.5
TRUST 6	2002	666	0.5	96.2
TRUST 7	2003	523	1	93.9
TRUST 8	2004	992		94.3
P. mirabilis				
TRUST 4	2000	430	2	94.0
TRUST 5	2001	366	2	90.7
TRUST 6	2002	523	4	88.1
TRUST 7	2003	520	8	85.4
TRUST 8	2004	963		84.3
S. marcescens				
TRUST 4	2000	161	2	94.4
TRUST 5	2001	127	2	92.1
TRUST 6	2002	173	2	91.9
TRUST 7	2003	172	2	92.4
TRUST 8	2004	320		93.4
C. freundii				
TRUST 5	2001	107	2	91.6
TRUST 6	2002	127	2	90.6
TRUST 7	2003	141	8	80.9
P. aeruginosa				
TRUST 4	2000	404	>8	73.0
TRUST 5	2001	514	>8	66.0
TRUST 6	2002	998	>8	67.7
TRUST 7	2003	882	32	65.3

TRUST 8	2004	1666		63.3
S. maltophilia				
TRUST 4	2000	94	0.5	79.8
TRUST 5	2001	110	0.5	79.1
TRUST 6	2002	150	0.5	85.3
TRUST 7	2003	163	1	78.5
TRUST 8	2004	299		77.3
H. influenzae				
TRUST 4	2000	1934	0.015	100%
TRUST 5	2001	1533	0.015	100%
TRUST 6	2002	1417	0.015	99.9%
TRUST 7	2003	1212	0.03	100%
TRUST 8	2004	1207		99.7%

- **Resistance Patterns**

Pearce et al (IDSA 2004) evaluated resistance trends among *E. coli* (n=1,568) to ampicillin, trimethoprim-sulfamethoxazole, and levofloxacin from 1999-2004. The isolates were from female outpatients with urinary tract infections. When data from all years wee combined, resistance among *E. coli* to ampicillin, trimethoprim-sulfamethoxazole, and levofloxacin were 39.5%, 20.5% and 3.1%, respectively. The authors concluded that resistance to levofloxacin alone was rare (0.06%), which indicates that when fluoroquinolone resistance is found, it is most likely in strains that are already resistant to ampicillin and trimethoprim-sulfamethoxazole.

5. PHARMACOECONOMICS/OUTCOMES EVALUATION

A. PHARMACOECONOMIC ANALYSIS OF LEVOFLOXACIN THERAPY FOR CAP.

In the managed care era, it is important that physicians understand not only the clinical efficacy of individual therapies, but also their associated costs and economic benefits. To determine this information, pharmacoeconomic analyses are used to compare the total costs associated with different treatment regimens, including their effects on the quality of patient care.

For levofloxacin, cost-benefit analyses have focused specifically on its use as a treatment for CAP. This focus on CAP reflects the clinical and economic impact of the disease. CAP remains a common medical problem, with over 4 million cases diagnosed each year in the US. It is the sixth most common cause of death overall and it remains the most common cause of infection-related death in the US, with a case fatality rate of 8.8%. Present US estimates suggest that there are 10 million physician visits for CAP annually, resulting in 500,000 hospitalizations and 45,000 deaths (Siegel et al., *Clin Chest Med*.1996).

Two studies have been carried out that directly compare the cost-effectiveness of levofloxacin therapy and cephalosporin therapy for the treatment of CAP. These two pharmacoeconomic analyses were based on data from a Phase III clinical efficacy study in which CAP patients were randomly assigned to one of two treatment groups: those receiving levofloxacin (IV or PO), and those receiving ceftriaxone (IV) and/or cefuroxime axetil (PO) (File et al., *Antimicrob Agents Chemother*. 1997). In the clinical trial, a total of 310 patients were enrolled as outpatients and 280 as inpatients. Among the clinically assessable patients in the trial, it is important to note that more achieved successful clinical outcomes with levofloxacin than with cephalosporin therapy (96% vs. 90%, $P<0.05$).

The objective of the first study was to compare the CAP-related costs of levofloxacin therapy and cephalosporin therapy for inpatients. To maximize the power of the comparisons, the study specifically compared only those sub-populations of patients from the clinical trial who received either IV levofloxacin or IV ceftriaxone as initial primary therapy. Overall, 178 inpatients were included in the economic evaluation, 89 of whom received IV levofloxacin and 89, IV ceftriaxone. Data on the following categories of resource utilization were collected during the study: study medication use, other antimicrobial use, concurrent medication (non-antimicrobial) use, and outpatient, emergency department, and hospital care.

Table 1 shows the mean total cost estimates, by treatment, as well as those for several component cost categories. Patients initially treated with IV levofloxacin showed a statistically significant lower mean total cost over those initially treated with IV ceftriaxone, with the total cost for the levofloxacin group being 19% lower than that of ceftriaxone. In the component cost category of study medications, the IV levofloxacin group showed a statistically significant cost advantage. Other cost categories also

tended to show cost advantages for Therapy for CAP levofloxacin, but not at the conventional significance levels (i.e., P<0.05).

Table 1. Mean total per-patient costs of levofloxacin versus two cephalosporins for inpatients and outpatients treated for CAP

Cost Category	Levofloxacin (L)	Cephalosporin (C)	Difference (L-C)	P-Value
Inpatients				
Study medications	195	388	-193	0.0001
Other antimicrobials	66	124	-58	0.055
Concurrent medications	21	33	-12	0.083
Outpatient visits	228	218	10	0.696
Emergency departments visits	98	108	-10	0.684
Hospitalizations	5404	6551	-1146	0.086
Total Costs	6012	7422	-1410	0.048
Outpatients				
Study medications	92	178	-86	0.0001
Other antimicrobials	7	9	-2	0.473
Concurrent medications	7	5	2	0.294
Outpatient visits	451	419	32	0.100
Emergency departments visits	102	131	-29	0.280
Hospitalizations	1	141	-140	0.080
Total Costs	660	883	-223	0.008

*Numbers are from sensitivity analysis; †expressed in $US 1997; ‡compares IV levofloxacin with IV ceftriaxone as initial primary therapy for patients hospitalized with CAP; §compares PO levofloxacin with PO cefuroxime axetil as initial primary therapy for patients treated as outpatients for CAP.

Greater than 17% of the total cost savings associated with levofloxacin was accounted for by its cost reductions in the categories of study medication costs (mean cost reduction, $193) and other antimicrobial costs (mean cost reduction, $58). Much of this was due to levofloxacin's lower cost for daily treatment, which (as the unit prices were very similar) was largely the result of once daily dosing of IV levofloxacin compared with once- or twice-daily dosing of IV ceftriaxone. Also of some importance may be the earlier switch to PO treatment observed with levofloxacin (3.19 vs. 3.41 days after initial IV treatment). The bulk of the remainder of levofloxacin's cost savings was accounted for by a difference in mean costs of hospitalization ($1,003), which accounts for 81% of the total cost difference between the treatment groups. This was largely based on the differential (in favor of levofloxacin) in both hospital and intensive-care unit lengths of stay along with their associated resource utilization (Rittenhouse et al., *P and T*. 1999).

The objective of the second study was also to compare the CAP-related costs of levofloxacin therapy and cephalosporin therapy, but this time exclusively in outpatients. To accomplish this, component and total costs were compared in two outpatient sub-populations: those who received PO levofloxacin therapy, and those who received PO cefuroxime axetil. Again, these economic data were derived from a clinical trial comparing the clinical efficacy of levofloxacin vs. cephalosporins.

The levofloxacin treatment group demonstrated a total cost advantage over cefuroxime axetil (mean advantage, $169), although this advantage did not rise to the level of statistical significance *(*P=0.094). Study medications were less expensive in the levofloxacin group than in the cefuroxime axetil group (mean advantage, $86), which was statistically significant *(*P=0.0001). Mean cost estimates for three of the other five cost categories also indicated advantages for the levofloxacin treatment group, but not at statistically significant levels (Rittenhouse et al., *Am J Managed Care*. 2000).

An additional study was conducted to investigate the pharmacoeconomics and clinical implications of levofloxacin 750 mg for 5 days for CAP (Milkovich et al., Poster presented at the 11th ICID, 2004). The study compared levofloxacin 750 mg IV or PO for 5 days to levofloxacin 500 mg IV or PO for 10 days. Patients receiving 750 mg levofloxacin were switched more rapidly from IV to PO therapy (a median of 2.35 days for the 750 mg group versus 2.75 days for the 500 mg group in the intent-to-treat population, P= 0.98).

Table 2. Number and cost of doses for the intent-to-treat subjects who completed therapy.

Patient	Characteristic	500 mg	750 mg	*P* value
IV	Number of patients	96	99	
	Number of doses (mean)	3.52	2.85	
	Cost per patient (mean ± SD)	$154.28 ± 94.30	$165.67 ± 74.02	
Oral	Number of patients	212	216	
	Number of doses (mean)	8.59	4.08	
	Cost per patient (mean ± SD)	$83.62 ±19.08	$48.09 ± 15.58	
All	Number of patients	216	232	
	Cost per patient (mean ± SD)	$150.65 ± 77.15	$115.47 ± 75.95	<0.001

[a]Cost per dose 500 mg IV= $43.82; 500 mg po= $9.73; 750 mg IV= $58.16; 750 mg po= $11.79
[b]Patients treated initially with IV levofloxacin
SD= Standard Deviation

B. OTHER FACTORS THAT INFLUENCE THE COST-EFFECTIVENESS OF CAP THERAPY

Antimicrobial costs have an important influence on the overall costs for CAP treatment. Another critical factor for inpatients, however, is the cost of hospitalization. Several studies have directly examined the impact of this cost, while others have analyzed the medical and economic costs and benefits associated with methodologies that shorten length of stay.

- **Economic Impact of Length of Hospital Stay**

One prospective study specifically assessed the relation between length of hospital stay and daily medical care costs (Fine et al., *Am J Med*. 2000). The median total cost of hospitalization for 982 CAP inpatients in the study was $5,942, with a median daily cost of $836. This median daily cost included $491 (59%) for room and $345 (41%) for non-room costs. Average daily non-room costs were 282% greater on the first hospital day, 59% greater on the second hospital day, and 19% greater on the third day than the average daily cost throughout the hospitalization. The high initial costs were attributed to use of the emergency department, radiology tests and procedures, and laboratory tests and procedures, which occurred more often during the initial stages of hospitalization. Subsequent analysis projected a mean savings of $680 for a 1-day reduction in length of hospital stay.

In another prospective randomized study, an analysis was performed that examined the cost benefits of a shortened course of IV antibiotic therapy for inpatients with CAP (Siegel et al., *CHEST*. 1996). Patients were randomized (1:1:1) to 1 of 3 treatment groups: Group 1 received 2 days of IV and 8 days of oral therapy; group 2 received 5 days of IV and 5 days of oral therapy; and group 3 received 10 days of IV therapy. The antibiotics used in the trial were cefuroxime for the IV course and cefuroxime axetil for the oral therapy.

No differences were found in the clinical course, cure rates, or resolution of chest radiograph abnormalities among the three groups. However, a significant difference was found in the length of hospital stay among the three groups. The mean length of stay was 6 ± 3 days in-group 1, 8 ± 2 days in-group 2, and 11 ± 1 day's in-group 3. The authors of the study estimated that the shortened length of stay could potentially save $2.9 billion per year for the US private sector.

Henneke et al presented a retrospective and prospective hospital-based study of non-intensive care admissions in patients with a diagnosis of pneumonia or complicated chronic obstructive pulmonary disease (COPD) initially treated with IV levofloxacin. Over a 3-month period, patients were evaluated by the pharmacist for appropriateness of oral therapy with levofloxacin and results were compared to the same months from the previous year. The primary outcome measure was decreased length of stay (LOS). Other outcome measures included a decrease in the number of IV doses of levofloxacin and cost of therapy. Patients were divided by age ($\geq$65 and <65 years). Pharmacist intervention logs showed that 50% of patients were changed to oral levofloxacin. The

pharmacist intervention group for patients ≥65 years of age had significant decreases in LOS from 8 days to 5.9 days, increasing hospital revenue by approximately $830,000. For patients <65 years of age the LOS was not significantly different (Henneke et al., *ASHP Mid Year Clinical Meeting* 2001).

Davis conducted a retrospective, computer-generated analysis (2000-2001) of patients admitted to the hospital with simple pneumonia and comorbidities. Patients were stratified to receive either oral levofloxacin only (PO), or any intravenous therapy (IV). Length of stay (LOS), severity of illness, hospital costs, death rate, and readmission rate within 30 days were compared. A total of 1068 patients were included in the analysis (568 in the PO group and 500 in the IV group). The average LOS was 3.09 ± 1.90 days for the PO group, compared to 4.00 ± 2.90 days for the IV group ($p< 0.0001$). On a scale of 1-4, the severity of illness for the PO group was 2.39 versus 2.57 for the IV group ($p<0.0001$). Average total cost was $2,893 ± $1,817 for the PO group compared to $3,921 ± $2,925 for the IV group ($p<0.0001$). The mortality rate was significantly lower for the PO group than the IV group (1.4% versus 5.4%, respectively, $p<0.001$), while the readmission rate was not significantly higher in the PO group (1.58% verus 0.80%, $p= 0.24$). A subgroup analysis for each severity of illness class indicated that the PO group had equivalent or lower LOS and costs compared to the IV group with similar mortality and readmission rates. Total expenditure for three antibiotics (levofloxacin, ceftriaxone, and cefotaxime) declined $213,400 over a 2-year period. The author concluded that initial oral levofloxacin therapy reduces LOS, total costs, and mortality compared to intravenous therapy (Davis CW, *Annual Meeting of IDSA* 2003).

These results imply even greater savings would occur if a higher percentage of patients could be treated exclusively as outpatients. It has been estimated that as many as 67% to 85% of patients who present to the physician with CAP are sent home from the emergency room, clinic, or office to be treated as outpatients, without a hospital stay (Fine et al., *Arch Intern Med*. 1997). However, the desire to treat patients on an outpatient basis, or to release patients from the hospital early, must be counterbalanced by concerns for their safety, and should never be attempted unless the patient is clinically stable.

- **Critical Pathways**

Since approaches to the diagnosis and treatment of CAP vary in different institutions, the utilization of resources for this condition also tends to differ widely across the health-care system. In an effort to help rationalize CAP therapy and maximize its resource utilization, one randomized prospective study examined the impact of a critical pathway on clinical efficacy and resource utilization in Canadian hospitals (Marrie et al., *JAMA*. 2000).

Critical pathways are management strategies that define essential steps of complex processes and optimize decision-making at these key points. The critical pathway used in the CAP study consisted of three components: 1) use of a clinical prediction rule to assist in the decision to treat on an inpatient or outpatient basis; 2) use of levofloxacin;

and 3) practice guidelines for the care of inpatients. The latter guidelines consisted of criteria for switching from intravenous to oral antibiotics.

Quality -of-life measurements, as well as the occurrence of complications, readmission, and mortality, were not different among patients treated by the critical pathway when compared to those treated by conventional approaches. However, use of the pathway was associated with a 1.7-day reduction in bed days per patient managed (4.4 vs. 6.1 days; P=0.04) and an 18% decrease in the admission of low-risk patients (31% vs. 49%; P=0.01). Although inpatients treated according to the clinical pathway had more severe disease than those treated by conventional approaches, they required 1.7 fewer days of intravenous therapy (4.6 vs. 6.3 days; P=0.01). Overall, the critical pathway produced cost savings that ranged from $457 to $994 per patient (Palmer et al., *Clin Therapeut*. 2000). Implementation of the critical pathway therefore reduced the use of institutional resources, and decreased overall treatment costs, without causing adverse effects on the well being of patients.

Kuti et al conducted a prospective study to evaluate the economic and clinical outcomes of a proactive pharmacist-managed IV to PO conversion program for levofloxacin. The following predetermined conversion criteria were proposed by these authors for pharmacists to identify candidates eligible for IV to PO conversion:

- temperature of <38.3^{o}C (101 ^{o}F) for at least 24 hours
- heart rate of ≤ 100 beats per minute for at least 24 hours
- respiratory rate of ≤ 24 breaths per minute for at least 24 hours
- systolic blood pressure of >90 mm Hg (with the patient not receiving pressor therapy) for at least 24 hours
- the ability to tolerate oral medications or a full liquid, general liquid or regular diet.

A prospective observational study (POS) assessing the standard of care was conducted over two months and was compared with the proactive conversion program (PCP). In the POS, patients receiving levofloxacin IV were followed daily by two pharmacists for data collection, but no recommendations were made to physicians to convert patients to the oral formulation. In the PCP, all patients receiving levofloxacin IV who were not in the intensive care unit and met the above conversion criteria were converted to oral levofloxacin by a staff pharmacist. Of all 131 patients in the study, 30 (60%) in the POS and 53 (65%) in the PCP met conversion criteria while receiving levofloxacin therapy. Conversion results and cost analyses for all patients who met the criteria for oral conversion are provided in the table below.

	POS (n=30)	**PCP (n=53)**	**P**
Conversion Data			
Mean day to meet criteria[a,b]	2.03±1.22	2.04±1.39	0.936
No. (%) of candidates converted	11 (37)	49 (92)	0.009
Mean day of conversion[a,b]	7.09±5.79	3.65±1.58	0.010

Mean no. of days of IV therapy[b]	6.50±4.89	2.89±1.85	<0.001
Mean no. of days of PO therapy[b]	1.50±2.79	3.47±3.24	<0.001
Median length of stay	9.5	6	0.031
Cost per patient ($)[c,d]			
Level 1 cost[b]	133±94	77±42	0.001
Level 2 cost[b]	151±105	91±46	0.002
Level 3 cost[b]	17,198±10,482	13,391±10,096	0.021

[a]The first day of levofloxacin therapy was called day 1.
[b]Mean ± standard deviation
[c]Level 1=levofloxacin acquisition costs; Level 2= level 1 costs plus costs directly related to antimicrobial use (supplies, preparation administration) and treatment of adverse effects; Level 3 = Level 2 costs plus the costs of hospital stay)
[d]In the intent to treat analysis (n=131), only level-1 costs were significantly less for the PCP compared to the POS.

Of the 53 patients who were candidates for oral conversion, 30 were clinically evaluable; the clinical success rate in these patients was 100%. Additionally, no patient in either group had adverse events associated with levofloxacin IV or PO. Of note, two patients in the PCP were switched back to levofloxacin IV due to non infection-related complications. The authors concluded that a pharmacist-managed proactive conversion program for converting levofloxacin therapy from IV to PO without physician approval reduced length of stay and institutional healthcare costs without compromising clinical outcomes (Kuti et al., Am J Health-Syst Pharm 2002).

Milkovich conducted a drug utilization study at the INOVA Health System to compare the clinical and economic outcomes among 2200 patients with CAP or other infections treated with ciprofloxacin or levofloxacin. Two implementation strategies were compared: a mandated switch from ciprofloxacin to levofloxacin termed therapeutic equivalency interchange (TEI) and a pharmacist recommendation to the physician about the preferred agent initiative referred to as standard educational tools (SET). The study objectives were to establish therapeutic equivalency between the 2 quinolones, compare the costs associated with treatments, and assess the best method for changing antibiotic prescribing patterns. Both levofloxacin and ciprofloxacin were successful in approximately 80% of patients and both agents were well tolerated. Levofloxacin was more often associated with treatment success when used as monotherapy compared to ciprofloxacin (48.7% vs. 32.01%, respectively, p=0.001). The economic analysis showed that the TEI was associated with greater cost savings than the SET ($60.10 vs. $37.30, respectively, p<0.001). The TEI strategy resulted in savings of $60.10/patient and annual future savings of $150,000. The author concluded that using TEI to implement conversion from ciprofloxacin to levofloxacin preserved patient care and demonstrated supplemental economic benefits to both the patient and healthcare organization (Milkovich, *Pharmacotherapy*, 2001).

- **Additional Information**

Enzweiler et al conducted a large study to assess the projected cost of therapy with three currently marketed fluoroquinolones in five patient populations, each with a

different distribution of renal function. Total cost of therapy included: administration costs, acquisition costs for levofloxacin (based on AWP), as well as personnel costs and IV administration sets (for non-premixed IV formulations only). A 10-day regimen was assumed for all drugs to standardize the analysis. Moxifloxacin was more expensive across all populations compared with gatifloxacin and levofloxacin ($p< 0.04$). No significant differences among cost of therapy for the oral drugs within a population were found, and levofloxacin was the least expensive in the IV formulation. Overall, potential cost savings are large for levofloxacin and gatifloxacin, based on manufacturers' dosage guidelines for patients with impaired renal function.

Richerson et al conducted a cost-effective analysis comparing IV monotherapy with either levofloxacin or azithromycin against cefuroxime and erythromycin among inpatients, using decision analysis techniques. When considering drug acquisition costs only, levofloxacin was the most expensive of the three regimens. When the costs of supplies, administration, adverse drug events and treatment failures were included in the analysis, levofloxacin and azithromycin were found to be similar in cost per pneumonia cure ($208 vs. $228). The authors state that under all plausible scenarios, azithromycin and levofloxacin, when used as monotherapy, were more cost-effective than the cefuroxime/erythromycin combination (Richerson et al., *Infect Dis Clin Pract.* 1998).

- **Summary**

Levofloxacin use for the treatment of CAP has been shown to be less costly, primarily based on acquisition costs, than two standard cephalosporin regimens, while still exhibiting similar or superior clinical efficacy. Strategies to limit length of hospital stay among CAP inpatients, which include the use of appropriate clinical pathways and appropriate conversion from IV to PO formulations, can also significantly decrease the costs of CAP therapy.

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7. INTENDED INDICATION

- Supplemental New Drug Applications (NDAs) have been filed with the Food and Drug Administration (FDA) for the following:

  Short-Course Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)